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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

FEBRUARY, 1926

ORIGINAL ARTICLES.

STUDIES OF THE VASCULAR CHANGES IN CASES OF POLYCYTHEMIA VERA.

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AND

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The physiological factors which are disturbed in polycythemia vera are chiefly related to: (1) Augmentation of the volume of the circulating cells and the total volume of the circulating blood, and the consequent vascular accommodation; (2) increased viscosity of the blood; (3) organic disturbances in the bloodvessels; (4) secondary thrombotic processes; (5) pathological changes in the erythrogenetic tissue; (6) disturbances in metabolism, related to heat, water and mineral balances.

The factors concerned with the adjustment of the vascular system to increase in volume and variations of the volume in the different stages of the disease are of extreme interest. In this disease, the effects, which a persistently large volume of blood with a relatively greater increase in its cell content than in its plasma content has on the circulatory system, can be studied. In a previous report[1] the relationship between the size of the capillaries of the skin and the volume of the blood was discussed. It was shown that the capillaries and the venules of the skin have a storage function under stress, and that the capacity for this storage is provided by the distention and, as has since been demonstrated, the utilization of all the available capillaries of the skin. The accommodation of

the bloodvessels to the increase of blood volume in polycythemia vera apparently occurs first in the vascular internal organs, the spleen and the liver and in the large veins. With progression of the disease and greater increase of the blood volume, the peripheral veins, and eventually the venules and capillaries of the skin, take part in the accommodation. It was observed that in older patients capillary distention did not extend into the arterial segments of the capillaries, as it did in the younger persons. The distention of the capillaries and venules is frequently extreme, which explains in part the changes in the color of the skin and mucous membranes so characteristic of this disease. The capillaries can often be recognized macroscopically in the nail-fold as fine red streaks. There is retardation of the flow in the capillaries, with a tendency toward stasis and peripheral cyanosis from cold. The disease on this basis is an erythrosis with a marked tendency toward cyanosis.*

Studies have been made in a larger group of cases (14) during 1924, with relation to: (1) Correlation of vascular distention and the degree of increase in the volume of blood; (2) comparative studies of the color of the skin, the capillaries and the blood volume; (3) arterial, venous and capillary pressures; (4) renal function; and (5) basal metabolism.

Eight of the patients in this group were males and 6 were females. The average age was fifty-one years. The youngest was thirty-seven and the oldest sixty-three. There was no particular relationship to geographical distribution. Two of the patients came from mountainous districts, but the majority were from the middle west.

Hemoglobin and Erythrocytes. The erythrocyte count was increased in every case, and the range varied from 5,500,000 to 9,050,000 for each cubic millimeter, the average for the group being 6,890,000. The hemoglobin varied from 142 to 160 per cent by the acid-hematin method, and averaged 152 per cent. In grams of hemoglobin for each 100 cc. of blood the range varied from 16.8 to 23 and averaged 21.†

Viscosity. Estimations of the viscosity of the blood have been made as a routine in all cases by means of the Hess viscosimeter. The normal ratio of water to blood is 1 to 4.5. A ratio of 1 to 5 has been accepted as the upper limit of normal. A very marked increase in viscosity was present in all cases. A return to normal occurred only with the development of a subnormal red cell count

* Lundsgaard and Van Slyke found a normal oxygen saturation of the arterial blood in a case of polycythemia vera. We have verified this in 3 cases. They note that the patients become cyanosed very readily in this disease. This they explained on a twofold basis: (*a*) the increased hemoglobin content, which magnifies the influence on capillary unsaturation; (*b*) increased width, and number of skin capillaries. We would call attention to another factor, the retardation of capillary flow due to increased viscosity and capillary distention.

† The normal value is 13.8 gm. according to the Haldane standard; 15.6 (Haden); 16.8 (Williamson).

TABLE I.—BLOOD VALUES IN POLYCYTHEMIA VERA.

Case.	Age, Sex.	Date.	Treatment remarks.	Height, cm.	Weight, kg.	Surface area, sq. m.	Plasma.			Hematocrit.		Total blood.			Erythrocytes.		Hemoglobin.	Viscosity (normal 1:4.5).
							Volume, cc.	Cc. for each mg.	Cc. for each meter of surface area.	Erythrocytes, per cent.	Plasma, per cent.	Volume, cc.	Cc. for each mg.	Cc. for each sq. m.	No. per cu. mm. millions.	Per cent.	Gm. for each 100 cc blood.	
1	56	6–30–24	.....	185	70	1.92	4340	61	2260	70	30	14,650	209	7640	6.05	166	22.9	1: 9.8
	M.	8–16–24	Bleeding and roentgen-ray	....	70	....	4440	63	2310	40	60	7,400	105	3860	.....	...	....	1: 5.8
2	61	.....	.....	164	53	1.57	3430	64	2180	58	42	8,170	154	5200	6.63	152	20.9	1: 8.5
	F.	.....	.....	...	..	....	....	..	....	..	..	.....	...	....	8.31			
3	47	.....	.....	170	62	1.72	3950	64	2300	65	35	11,300	182	6570	8.93	145	20.0	1:11.2
	M.	.....	.....	...	..	....	....	..	....	..	..	.....	...	....	8.90			
4	51	4–28–24	.....	174	63	1.76	4800	76	2730	60	40	12,000	190	6820	6.40	145	20.0	1:10
	M.	6–10–24	Bleeding and roentgen-ray	....	..	....	4500	71	2560	51	49	9,200	146	5220	6.11	121	16.8	1: 6.2
5	37	4–14–24	.....	172	50	1.58	4500	90	2850	57	43	10,460	209	6620	6.22	142	20.0	1: 9.6
	F.	5–20–24	Bleeding and roentgen-ray	....	50	....	3600	72	2280	50	50	7,200	144	4550	5.84	130	18.0	1: 7.1
6	42	.....	.....	164	60	1.65	2710	45	1640	62	38	7,100	126	4300	6.67	154	21.0	1:10
	F.	.....	.....	...	..	....	....	..	....	..	..	.....	...	....	6.41			
7	63	7–11–24	.....	174	73	1.88	3430	47	1820	60	40	8,570	117	4560	5.50	145	20.4	1: 7.4
	M.	7–31–24	.....	...	74	1.89	4140	55	2190	59	41	10,100	136	5350	6.90	142	19.8	1: 5.8
		8–20–24	.....	...	73	1.90	3560	48	1870	47	53	6,720	89	3530	.....	145	20.3	
8	44	.....	.....	190	59	1.82	3710	63	2040	62	38	9,760	165	5360	7.41	160	24.0	1:10.2
	F.																	
9	42	.....	.....	182	81	2.1	3750	46	1780	67	33	11,350	140	5400	7.55	170	23.0	1:12
	M.	.....	.....	...	..	....	....	..	....	..	..	.....	...	....	8.58			
10	52	.....	.....	159	50	1.5	3330	66	2220	56	44	7,570	150	5040	5.57	141	20.0	1: 7.6
	F.																	
11	59	12–29–23	Bleeding and roentgen-ray	185	68	1.9	4340	63	2270	60	40	10,840	160	5700	7.15	155	21.0	1: 9.4
	M.	1– 7–24		...	68	1.9	4500	66	2370	55	45	10,000	147	5280				
		6–17–24	.....	...	..	....	5000	73	2630	30	70	7,140	105	3750	....	83	11.5	1: 3.7
12	55	.....	.....	153	54	1.5	2860	52	1900	59	41	9,200	170	6140	9.11	142	20.4	1: 9.8
	F.	.....	.....	...	..	....	....	..	....	..	..	.....	...	....	9.05			
13	50	.....	.....	185	70	1.92	4240	60	2200	65	35	12,100	172	6300	5.50	155	21.3	
	M.	.....	.....	...	..	....	....	..	....	..	..	.....	...	....	6.60			
14	62	12–15–24	.....	177	60	1.75	3640	60	2070	67	33	11,000	183	6280	7.85	165	22.5	1:13.2
	M.																	
		Average	values				3800	60	2160	62	38	10,300	166	5850	6.89	152	21.0	1:9.9

TABLE II. DATA RELATIVE TO VASCULAR SYSTEM IN POLYCYTHEMIA VERA.

Case.	Age, Sex.	Blood-pressure.		Peripheral veins.	Peripheral arteries.	Retinal vessels.	Heart.	Electrocardiographic findings.	Splenic enlargement.	Hepatic enlargement.	Data relating to size of capillaries of the skin.	Symptoms referable to vascular system.
		Systolic.	Diastolic.									
1	56 M.	155 170	110 90	....	....	Veins full and dark, exaggeration of arterial reflex, arteriovenous compression	Enlarged 2	Diphasic T in Lead I	3	2	Long loops with distention 2 of venous limbs, relative contraction of arterial limb; 33 per cent. of loops tortuous	Dyspnea and substernal distress on exertion. Mental apathy. Increasing redness of skin.
2	61 F.	124	82	Not abnormal	.....	Veins full and dark	Not enlarged	....	Hard 2	2	Short loops. Distention 3 of venous limbs. Relative contraction arterial limb; 90 per cent tortuous loops	Hematuria, hematemesis, vertigo.
3	47 M.	145	95	....	Feeble pulsation in vessels of right leg	Negative	Not enlarged	....	3	0	Short loops. Venous engorgement 2	Claudication in right leg sign of arterial blocking. Painful attacks of cyanosis in second and third fingers of right hand.
4	51 M.	130	95	Hemorrhoids 1	.....	Retinal veins full and dark. Contraction of arteries	Not enlarged	....	2	2	Dilatation 2 of venous loops. Moderate contraction of arterial loops; 15 per cent tortuous loops. Many open capillaries	Fatigue and weight loss, only symptoms.
5	38 F.	125	85	Varicose veins both legs	.....	Veins large and dark	Not enlarged	....	3	1	Venous enlarged 1; 25 per cent of loops tortuous	Moderate vertigo, fatigue, loss of weight 10 pounds. Increased color in face.

legs

6	42 F.	120	80	Hemorrhoids	.....	Negative	Not enlarged	Negative	2	1	Arterial and venous limbs engorged 2; 10 per cent of loops tortuous	Heightened color to skin for two years no dyspnea, vertigo 1+.
7	63 M.	140	106	.....	.....	Veins full, dark, contraction of arteries	Not enlarged	Negative	2	0	Engorgement 3 venous limbs contraction 2 of arterial limb	No dyspnea or vertigo.
8	44 M.	128	68	.....	.....	.....	Negative	....	1	2	Distention 3 venous limbs, 2 arterial limbs, few hemorrhages	No dyspnea, vertigo or edema, gastric symptoms marked.
9	4? M.	135	98	Varicose veins	Throbbing carotids	Veins full, dark, tortuous	Negative	....	2	0	Distention 3 venous limbs. Contraction 1 arterial limb	Vertigo, weakness, intolerance to extreme heat or cold, deafness.
10	52 F.	122	64	.....	.....	Negative	Negative	Negative	2	0	Venous limbs engorged 3. Contraction 1 arterial limb	Melena, hematemesis. Exhaustion and headaches.
11	59 M.	182	106	.....	Calcified arteries of leg	Mild retinal arteriosclerosis	Pulse 120	Negative	1	0	Contraction 2 of long arteriosclerotic loops	Weakness, headaches. One cerebral seizure without paralysis.
12	55 F.	170	90	.....	Peripheral arteries sclerosed 2	.....	Enlarged 1, systolic mitral and aortic blow	....	2	0	Long capillaries, engorgement 3 of arterial and venous limbs	Dyspnea 2 on exertion, epigastric pains with fear of impending death.
13	50 M.	114	90	Dilatation smaller venules, hands and face	Calcified arteries leg	Veins full and dark	0	Negative	2 not hard	3	Marked distention of venous limbs, relative contraction of arterial limbs	Dyspnea 1, attacks left upper abdominal pain, infarct, (?) splenitis. (?)
14	62 M.	130	85	Marked dilatation, smaller venules	No evidence of arteriosclerosis	Veins full and dark, some arteriovenous compression	Negative	Negative	1	1	Marked distention, venous and arterial limbs	Dizziness, polyuria attacks, tachycardia, loss of weight; excessive appetite.

and normal percentage of cells by the hematocrit. Even with a normal red cell count the viscosity was frequently increased; it is, therefore, a very important diagnostic finding (Table I). The viscosity bears a closer relation to the percentage of cells by the hematocrit and the hemoglobin than it does to the erythrocyte count.

Blood Volume. The total volume of the circulating blood as determined by the dye method was increased in every case. The average value for the group was 10,300 cc., or 166 cc. for each kilogram, or 5850 cc. for each square meter of surface area.

The volume of the circulating plasma showed a range of from 46 to 90 cc. for each kilogram of body weight. The average amount was 60 cc. for each kilogram, or 2160 cc. for each square meter of surface area.

Hematocrit Readings. The percentage of erythrocytes as determined by the hematocrit‡ varied from 58 to 70 per cent, the average being 62 per cent.

The Arteries and Veins. In Table II correlative data with respect to the spleen, liver, peripheral veins, capillaries and arteries are given. The condition of the retinal vessels, the size of the heart, the relative size of the spleen and liver, and the condition of the capillaries of the skin are noted in each case.

At the time of admission the complaints were mainly those relating to the vascular system. In 2 cases (Cases IV and VI) hemorrhoids were the chief complaint; in 2 (Cases V and IX), varicose veins of the legs; in 5, symptoms relative to disturbances of the peripheral arteries, symptoms in 3 being those of claudication, and in 2 diminished pulsation in the vessels of the leg was found. Roentgenological examination showed calcification of the arteries of the leg in Cases XI and XIII.

Ophthalmoscopic examinations were made in 13 cases, and of these the characteristic retinal picture was observed in 9 (64 per cent). In 3 cases the ophthalmoscopic report was negative. The positive findings were fulness and dark color of the veins with or without tortuosity. In 5 cases venous distention and arterial contraction, exaggerated arterial reflex and arteriovenous compression were observed. In 1 case observations were made on the retinal vessels and skin capillaries during the course of treatment with phenylhydrazin hydrochlorid. Engorgement of these vessels had entirely disappeared when the total blood volume was reduced to approximately 105 cc. for each kilogram of body weight.

The Heart. The size of the heart was noted in every instance. Enlargement 1 or 2 was present in 3 instances (Cases I, III and XII).

‡ A weighed amount of 10 per cent sodium oxalate solution was evaporated uniformly on the inside of hematocrit tubes, thus assuring a uniform distribution. One cubic centimeter of 2 per cent oxalate in solution was employed as a control and there was an average variation of 1 per cent.

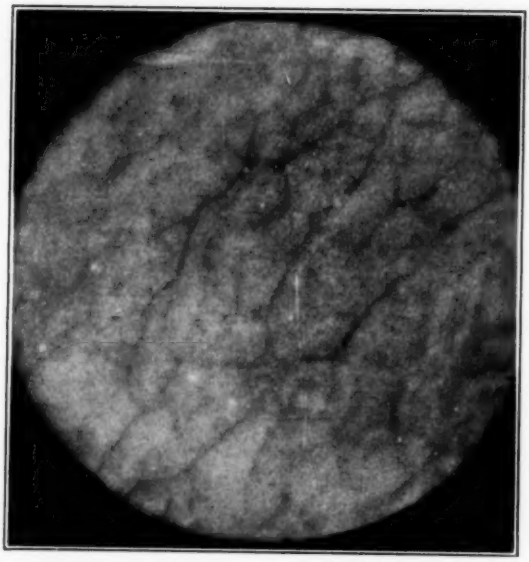

FIG. 1.—Photomicrograph of skin capillaries on back of hand in case of polycythemia. Note the large number of distended capillaries and venules in field. Only the tips of the loops are visible. × 25.

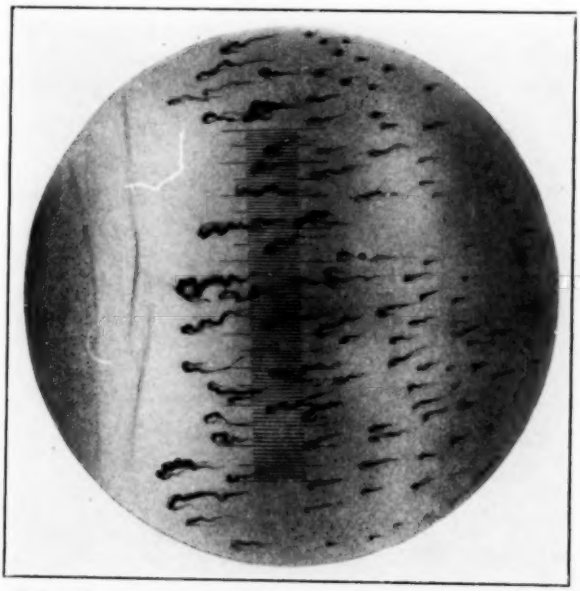

FIG. 2.—Polycythemia vera. Nail-fold capillaries. Sketch drawn to scale. Smallest division 0.01 mm. Note the distention of venous segment of capillary loop. Many loops in field. Blood volume 160 cc. for each kilogram of body weight.

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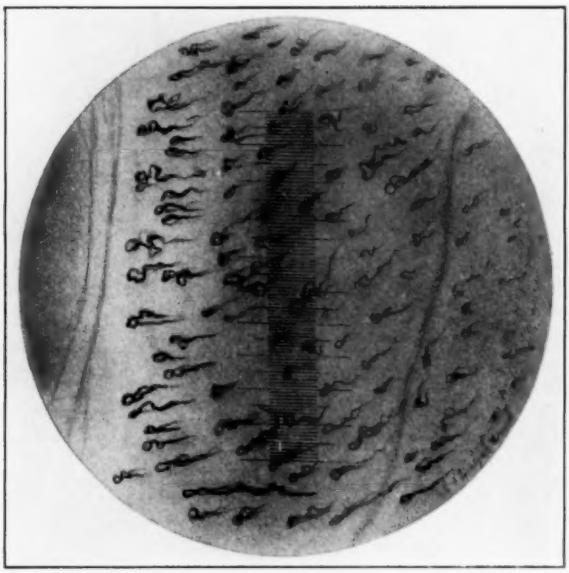

FIG. 3.—Polycythemia vera. Nail-fold capillaries drawn to scale. Loops less distended. Blood volume 137 cc. for each kilogram of body weight. Same case as in Figure 2.

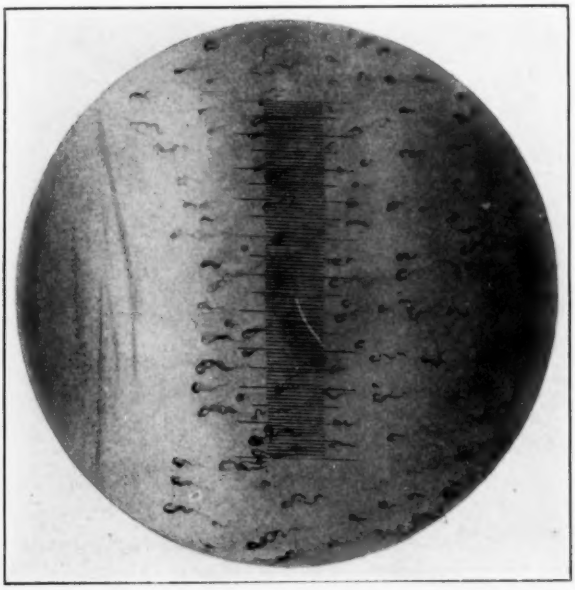

FIG. 4.—Polycythemia vera. Nail-fold capillaries drawn to scale. Capillary loops thin and difficult to see. There is a definite decrease in the number of open capillaries. Blood volume 99 cc. for each kilogram of body weight. Same case as in Figures 2 and 3.

There was no other evidence of cardiac disease except in Case XII, in which systolic mitral and systolic aortic murmurs were present. Electrocardiographic examinations were made in 6 instances, and no significant changes were present.

The Spleen. The spleen was enlarged in all the cases. In 3 the enlargement was graded 1; in 8, 2; in 3, 3. The spleen was usually firm and hard.

The Liver. The liver was enlarged in 8 cases, being graded from 1 to 3; in 6 the liver edge was not palpable.

The Capillaries. The capillaries of the nail-fold were examined in every case. Engorgements of the venous limb and collecting venules were graded 2 or 3 in 12 cases. Engorgement 1 or 2 of the arterial limb was noted in 4 cases. In 9 cases the arterial segment showed relative contraction. In Case VIII small capillary hemorrhages were seen. The percentage of tortuous capillaries, from 10 to 90, showed more relationship to age than to the degree of increase in the volume of the blood. A quantitative study of the number of open capillaries for each square millimeter of skin area was made in 2 cases; in Case XIV there was an average of 65 open capillaries for each square millimeter of skin on the back of the hand (Fig. 1). The average number in healthy persons varies from 15 to 40. The capillaries were studied in several cases during the course of treatment while a decrease in the total volume of the circulating blood was taking place (Figs. 2, 3 and 4). A progressive diminution in engorgement and number of open capillaries followed *pâri passu* the changes of volume.

Color Analysis of the Skin. Color measurement of the back of the hand, tongue or lower lip and cheek were carried out as a routine in 4 cases. The skin tintometer, as devised by Rowntree and Brown,[5] was used for direct color matchings. The tintometer values were originally standardized according to the Munsell system for color measurement.*

Direct color studies were made by the Munsell wheel and color disks for direct skin matchings. This is fairly satisfactory but is time consuming. There is some difficulty in matching flat colors to the live skin color, but fairly accurate comparisons were made. Checked readings by different observers have shown a range of error up to 20 per cent, which is low as compared with ordinary clinical methods. Color analyses have been made in other cases and are now being made as a routine.

* The Munsell system of color measurement employs a series of color disks with perforations and slits allowing the disks to be superimposed, exposing various segments of each. The disks are then spun on a motor shaft, thus optically mixing the colors. Color according to this system is measured according to hue, value and chroma. The color measurements according to hue, value and chroma are printed on the back of each disk. Five primary and five intermediate hues are utilized. Hue is indicated by the color abbreviation as R = red, RP = red purple; value by the numerator, and chroma by the denominator of the fraction.

COLOR ANALYSES IN CASE V.

Area	Color readings.		Blood volume.	
Cheek	R 4/8	0.48	209 cc. for each kilogram.	
	P 3/3	0.38		
	YR 8/5	0.14		
			Color analysis in a normal blonde.	
Knuckle of right hand	R 4/8	0.37	R 7/5	0.33
	P 3/3	0.33	B 7/2	0.42
	YR 8/5	0.30	YR 8/5	0.25

Blood Pressure. The average arterial blood pressure in the 14 cases was 138 systolic and 90 diastolic. In Case I, XI and XII there was a mild hypertension with normal diastolic pressure and a moderately high pulse pressure.

The venous pressure was determined by the Hooker method in Case XIV, on the peripheral veins of the back of the hand at heart level. The average of six determinations was 15 mm. of water. This reading is slightly higher than normal.

The capillary pressures were determined in 1 case by the Danzer-Hooker method on the capillaries of the nail-fold. The values are expressed in millimeters of mercury and are approximately normal according to this method: Small capillary: 14, 12, 14; large capillary: 15, 17, 18.

TABLE III.—RENAL FUNCTION STUDIES IN POLYCYTHEMIA VERA.

Case.	Blood-pressure.		Urine.			Blood.		Phenolsulphonephthalein excretion in two hours, intravenously, per cent.
	Systolic.	Diastolic.	Albumin.	Casts.	Erythrocytes.	Urea mg. for each 100 cc.	Uric acid, mg. for each 100 cc.	
2	124	82	2	Hyaline and granular	0	..	....	45
4	130	95	3	Few leukocytes	1	30	....	30
7	140	106	0	Hyaline 1	0	..	....	45
8	128	68	1	0	0	47	4.9	40
9	135	98	3	Hyaline 1	0	..	....	50
11	182	106	2	Hyaline 1	0	28	3.8	
13	114	90	2	0	..	..	6.35	30
14	130	85	1	Granular 1	*	16	2.9	40

* Occasional.

Renal Function (Table III). The renal function was studied in 8 cases. Albumin, graded from 1 to 3, was present in all. Hyaline and granular casts were present in 6 cases. Erythrocytes were found in 1. The study of the chemistry of the blood showed slightly elevated blood urea in Case VIII. In Case XIII, a patient in whom there were clinical manifestations of gout, the blood uric acid was 6.35 mg. for each 100 cc. of blood. The excretion of

phenolsulphonephthalein in two hours was slightly decreased in 4 cases and moderately decreased in 2 (Cases IV and XIII). In the latter case signs of mild renal impairment were shown by the restricted range of specific gravity and by a definite lag in excretion of water according to the standard water test.

BASAL METABOLISM IN SEVEN CASES.

Case.	Rate.	Total blood volume, cc. for each kilogram.
5	+44	209
14	+37	183
13	+4	172
11	+9	160
9	+5	140
7	+22	136

The basal metabolic rate was increased in 3 cases and seemed to stand in some relationship to the higher levels of total volume of the blood.

Discussion. Most of the symptoms in polycythemia have a circulatory basis. From the standpoint of physiology the symptoms are of three types: (1) Those related to vascular distention and increased viscosity of the blood, as vertigo, sensation of fullness in the head, headache, hemorrhage and alterations in the color of the skin; this premise is borne out by the symptomatic improvement which follows a decrease in the volume of the blood and the number of cells; (2) those related to organic changes in the bloodvessels, either of an endarteritic or of a thrombotic nature, as infarction with localized pain (as splenitis); claudication and cerebral changes; and (3) those related to disturbances in metabolism, as loss of weight with excessive appetite, polydipsia, exhaustion and intolerance to heat and cold.

The symptoms due to distention are of the greatest interest because there is no other clinical condition so far as is known in which a persistent augmentation of the volume of the blood is present. The clinical symptoms produced by distention of the bloodvessels would, *a priori*, be most striking in relationship to the head. The headache in these cases is described as a generalized fullness and sensation of pressure and not as a throbbing pain. Vertigo is occasionally extreme, and at times change of position induces marked staggering. Hemorrhage occurs usually in the stomach or nose, less frequently in the brain, and rarely in the skin or kidney. Purpuric manifestations have not been observed. The relief from the cerebral symptoms afforded by bleeding, roentgenotherapy or by the use of phenylhydrazin hydrochlorid is striking. The symptomatic beneficial effects have been noted when there is a decrease approximating at least 25 per cent in the total volume of the blood. Complete relief is afforded when the volume is reduced to approximately 100 cc. for each kilogram of body weight. There is no direct

relationship between the severity of the symptoms and the degree of increase in the volume of the blood. The patients showing the largest volume of blood did not present symptoms of the distention type. Of the 6 patients with the largest volume of blood 4 presented symptoms of a general or metabolic type; 2 sought advice because of marked changes in the color of the skin, and 1 because of dizziness, polyuria and tachycardia.

There was apparently a relationship between the size of the spleen and the degree of increase in the volume of the blood. Three cases with the largest spleens (Cases I, III and V) also showed the largest volumes. The spleen was usually described as firm and rarely tender. In no case was there an extreme enlargement of the spleen similar to that observed in cases of leukemia. The liver was slightly enlarged, 2 and 3, in 7 cases. In only 1 instance was there an enlargement graded 3. No relationship existed between the degree of enlargement of the liver and the volume of the blood.

The appearance of the retinal veins is of interest and of diagnostic importance. The typical picture is that of distention of the retinal veins with or without tortuosity. They usually appear as full black streaks, and present a striking picture. Arteriosclerotic changes with contraction of the retinal arteries were present in 5 cases. The latter seemed to bear no relationship directly to the polycythemia, but more to the age and consequent degenerative changes in the vessels. Engorgement of the retinal veins was seen in 64 per cent of the cases, while typical engorgement of the venous portion of the skin capillaries was present in 92 per cent.

The response of the capillaries of the skin to the increase in the volume of the blood is twofold: Distention and enlargement of part or all of the capillary loop, and the opening up of all available capillaries. Krogh has shown in certain tissues that there is a relationship between the number of functioning capillaries and the metabolic requirement, and that at any given time under given conditions only a certain number of the capillaries are open. In polycythemia vera the capillaries and venules have an additional function, that of storage. The function of storage is effected not only by enlargement of these vessels, but by the use of all available capillaries. The reservoir function of capillaries and veins in experimentally increased volume of the blood has been shown by Meek and Eyster.[4] They found that 30 to 100 per cent of its volume may be added to the circulation without causing cardiac dilatation, while the capillaries and venules of the ear show dilatation and opening up of new channels.

In polycythemia vera, additional vascular space, is utilized with a loss or impairment of the physiological heat mechanism of the skin. The most important function of the skin is that of heat regulation. Cold produces a closure of many of the skin vessels with a decrease in the radiation of heat. When heat conservation

is unnecessary, and when heat dissipation is advisable, a large number of resting capillaries is available. In polycythemia this mechanism of heat regulation is impaired, since all available capillaries are continuously functioning. Many of the symptoms of polycythemia, such as intolerance to heat and cold, a burning sensation of the skin and the sense of suffocation, are made clear by this conception of the impairment of the mechanism of heat regulation. Engorgement and distention of the venous limb of the skin capillaries were found in all except 1 case, while enlargement of the arterial limb was present in only 3 cases. The capillaries could frequently be seen macroscopically in the nail-fold as fine lines. There is usually a sharp point of transition between the arterial and venous segments, which suggests an important difference in the structure and the response of these portions of the capillary loop to increase in the volume of the blood. The incidence of tortuous loops was related to the age of the individual rather than to the polycythemia. Capillary hemorrhages were seen in 1 patient. The response of the capillaries to the application of histamin and to mechanical stimulation was normal in 3 cases.

The absence of cardiac dilatation is striking and bears out the experimental data of Meek and Eyster on the cardiac measurements in experimentally increased volume of the blood in animals.

There is no demonstrable relationship between the systemic arterial blood pressure and the polycythemic type of increase in the volume of the blood. In only 3 patients of this series was there an elevation of systolic blood pressure and in these it was only of moderate degree. These findings agree closely with Lucas'[2] figures. The cases in his series, in which splenomegaly was present, showed fairly normal blood pressure. The diastolic pressure was not elevated proportionately, indicating that the peripheral resistance was not abnormal. It is apparent that increased viscosity and volume of the blood *per se* play a negligible part in the production of hypertension. The venous pressure, however, as would be anticipated, was increased in 2 cases in which it was tested. The capillary pressure according to the Danzer-Hooker method was normal; we could expect, however, that the application of a more accurate method, such as Carrier employed, would show at least some elevation of pressure in the venous segment.

Slight albuminuria was present in all cases, and hyaline and granular casts in most. The blood nitrogen was not elevated. The phenolsulphonephthalein excretion was definitely decreased in 2 cases. Polycythemia seems to exert no marked deleterious effect directly on the kidney.

Summary. Fourteen cases of polycythemia vera were studied in relation to the vascular readjustments to the increased volume of the circulating blood.

The total volume of the circulating blood was increased in all

cases. The average for the series was 166 cc. for each kilogram of body weight.

The viscosity of the blood was increased in all cases. The hematocrit values for the cells varied from 58 to 70 and averaged 62 per cent.

The capillaries of the nail-fold showed engorgement of the venous limb in 13 cases (92 per cent); of the arterial limb, in 4. There was complete utilization of all available capillaries of the skin.

Engorgement of the retinal veins was present in 9 cases (64 per cent). Engorgement of the skin capillaries and retinal veins disappeared when the total volume of the blood had diminished to approximately 100 to 110 cc. for each kilogram of body weight.

Determinations of skin color were made. The degree of cyanosis was determined quantitatively, and the color changes followed during the course of treatment.

Cardiac enlargement and cardiac disease were noticeably absent. The liver was slightly enlarged in 57 per cent of cases. The spleen was enlarged in every instance, and there was a distinct relationship between the splenic enlargement and the degree of increase in the total volume of the blood. There was no increase of blood pressure in polycythemia vera. The renal function was slightly impaired.

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EXPERIMENTAL CORONARY EMBOLISM.

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I. **Historical.** Although the importance of the coronary circulation in relation to the integrity of the heart has long been recognized,

a number of significant additions to our knowledge have been made within recent years.[8] These contributions cover the entire range of the blood supply to the heart, from the anatomic, pathologic and physiologic aspects. From the viewpoint of disturbed physiology, one of the most recent and suggestive papers is that of Bruno Kisch,[11] a student of H. E. Hering. In this paper Kisch discusses certain disturbances of cardiac function due primarily to interference with the blood supply of various areas of the heart. He emphasizes the need of exact knowledge of localization of the disturbances of the blood supply to the heart similar to the knowledge we possess of the disturbances of the blood supply to the brain. He speaks of the frequent sudden deaths of individuals suffering with advanced disease of the coronary vessels from sudden blocking of the blood supply of one of the larger coronary arteries, resulting in ventricular fibrillation—the "Sekunden-herztod" of Hering. He asks what are the results of disturbances in the coronary circulation not severe enough to produce fibrillation and death, and comments on the clinical importance of these minor disturbances resulting in a great variety of symptoms on an arteriosclerotic, infectious or other basis. He feels that this problem is best approached from the standpoint of animal experiment and cites a number of experiments with the perfused dog's heart, whereby he observed the effects of alternatingly clamping and unclamping different branches of the coronary arteries, obtaining four separate suspension curves from the heart chambers. By this means he found that clamping the left coronary artery in the perfused dog's heart resulted in alternation of the left ventricle with disturbances in the conduction system with partial or complete *A–V* block; clamping the right coronary resulted in alternation of the right ventricle but without disturbance in the conduction system. By the same experiment definite though less constant alternation of the auricles can be demonstrated, while clamping of the right coronary artery occasionally results in auricular fibrillation. Kisch comments on the fact that in dogs the conduction system is supplied for the most part by the left coronary artery while in man from the right vessel. In his conclusions he attempts to draw analogies between the results of these animal experiments and the clinical findings of angina pectoris, alternation of the heart, fibrillation of the auricles and ventricles, in patients suffering with disease of the coronary vessels.

The older methods of investigation of the coronary circulation consisted of more permanent obstruction to the bloodflow but likewise yielded valuable results. The first important contribution was made almost fifty years ago when Cohnheim and von Schulthess-Rechberg,[3] in 1881, ligated some of the larger branches of the left coronary artery in dogs, finding no change in pulse frequency and blood pressure for 30 to 40 seconds following ligation. Toward

the end of the first minute, however, the heart became definitely arrhythmic and slower and in approximately 105 seconds the apparently strongly beating heart suddenly became still, the auricle however, continuing regular pulsations. After 10 to 20 seconds of ventricular asystole, both ventricles began an active energetic fibrillation lasting 40 to 50 seconds, followed by permanent quiescence. Further contractions of the heart could not be elicited by any of various methods of stimulation and removal of the coronary ligature within 80 to 90 seconds was not effective in preventing the above sequence of events. The experimenters concluded this result was due to a particular heart poison elaborated as a result of the coronary artery closure.

Martin and Sedgwick,[12] Ferroglio and Drogoul,[7] Porter,[14] Hirsch,[9] and others, however, found variable results in repeating the above experiment, either a complete absence of stoppage of the heart or a marked prolongation of the time interval. As the most likely explanation of this variability in results, these investigators offer the physiologic importance of the anastomosis between right and left coronary arteries as well as the probable effects of mechanical trauma to the heart during the manipulation. When all mechanical trauma to the heart is controlled, the dog's heart will stand an anemia lasting from two and a half to three minutes without losing its ability to be restored with the reception of fresh normal blood.

The first study of the effects of ligating branches of the coronary artery on the electrocardiogram was made by Kahn in 1911,[10] who found a negative *T* wave after ligation of the septal artery of the dog. Smith,[17] in 1918, found in reference to the *T* wave, "a fairly constant change from the strongly positive peak to a markedly negative and then a slower return to the positive or isoelectric form" following ligation of any branch of the left coronary artery.

In addition to ligation of the coronary vessels, attempts have been made to study the effects of narrowing or partial closure of the coronary arteries, by the injections of solid materials. Panum,[13] in 1882, was the first to investigate the effects of experimental coronary embolism, by using an injection mass consisting of talcum, wax, oil and lampblack having a melting point of 40° C. Following the injection of all visible coronary vessels, the heart continued to beat intermittently for one and a half hours, thus demonstrating that the heart can withstand for a comparatively long time, partial closure of the coronary circulation.

See, Bochefontaine and Roussy,[16] in 1881, injected a suspension of lycopodium spores into the septal branch of the left and the entire right coronary artery, following which heart beats ceased in from 45 to 150 seconds. By the same method, Porter,[15] in 1896, injecting from the left carotid artery, all branches of the coronary circulation, found the heart irregular in 20 seconds, followed by a cessation of the heart beat with the development of a severe fibrillation.

Wassiliewsky[19] in 1911 injected a suspension of lycopodium spores in small portions so that only partial obliteration of the coronary circulation occurred. By this means the same animal could be injected two or three times; following the last injection the heart stopped approximately in two to five and a half minutes.

In general then the injection of lycopodium spores substantiates the results obtained by ligation. No studies of the effects of lycopodium spore injection upon the electrocardiogram have appeared in the literature.

Summarizing briefly the above observations, the results of partial or complete obstruction to the coronary circulation may be stated as follows:

(*a*) The dog's heart, several minutes after the abrupt exclusion of a considerable portion of the coronary circulation dies from want of blood (oxygen want? anemia?).

(*b*) The fatal outcome resulting from ligation of smaller-sized vessels results from accessory causes (trauma, hemorrhage, and so forth).

(*c*) The most characteristic symptom of an anemia of the heart from coronary obstruction is a more or less severe, outspoken and progressive weakness of the heart—ventricular fibrillation.

(*d*) The variability in the production of ventricular fibrillation following coronary artery obstruction is due to:

1. The size of the ligated or obstructed vessel.
2. The particular function of the area of the heart supplied by the vessel obstructed.
3. The type and degree of narcosis (more severe with morphin).
4. The extent and severity of associated hemorrhages.
5. The extent and severity of mechanical trauma.
6. The degree of local anemia (extent of collateral circulation).
7. Degree of local tissue poisons (CO_2).
8. The presence of abnormal foci of heart irritability.

II. **Purpose and Methods of Present Experiments.** The present experiments were planned with the view that the injection of minute solid particles into the coronary circulation with subsequent lodgment of these small particles (emboli) in the capillaries and arterioles, would more nearly approximate the clinical findings of coronary embolus than the ligation of larger branches. It was hoped that by the injection of a suspension of lycopodium spores, sufficient capillaries and arterioles might be occluded as to reproduce experimentally in dogs chronic interstitial myocarditis, not unlike that seen in man, the result of atheroma of the smaller capillary and precapillary vessels. We planned by this experiment to test the assertion of Aschoff, Mönckeberg and others that "practically all macroscopically visible scars of the heart muscle are the result of vessel occlusion, thrombotic or embolic in character and due to advanced atherosclerosis." We planned further, if such areas of

embolic fibrous myocarditis could be produced, to obtain electrocardiograms before and after their formation, and thus to correlate changes in the curves with the myocardial lesions.

The experiments we wish to report were carried out on a series of twelve dogs over a period of four months. A typical experiment may be described as follows: A preliminary electrocardiogram was taken as a control before interference of any sort—the dog being strapped to the operating board in the dorsal position. A preoperative hypodermic injection of ½ gr. of morphin was then given and after a short interval a second curve was taken to study the effect of the morphin. The dog was then etherized and a tracheal catheter inserted and connected to an electric blower or foot bellows. Each step in the experiment was controlled by an electrocardiogram, electrodes applied in the usual way to both fore legs and left hind leg, leads connected by distant wiring to the electrocardiograph in the Heart Station, while one of us (W. S. P.) was in constant communication by house telephone with the technician in the laboratory.

Incision of the chest was made parallel just to the left of the sternum, cutting the fourth and fifth costal cartilages and then enlarging the incision as required. As soon as the chest cavity was entered, intertracheal insufflation was started and anesthesia continued by this means until the chest was closed.

The pericardium was grasped with forceps and drawn up into the well-retracted wound. The pericardium was then split between the forceps and the heart thus lay exposed as in a sling of pericardium.

The descending anterior branch of the left coronary artery was readily discernible lying in its fatty epicardial covering over the interventricular septum. Sometimes it could be entered with no further dissection, at other times it had to be freed from the fatty tissue. We found that a hypodermic needle of the usual gauge, bent to an angle of 50 degrees, greatly facilitated the procedure.

In order to reach the posterior descending branch of the right coronary, the apex of the heart was pulled upward by gentle traction on the lower pericardium and the artery reached from behind, a certain amount of rotation being necessary.

To reach the vessels at the site of emergence from the aorta was more difficult, the fatty tissue covering the vessels was usually most marked in this location and always had to be dissected away before the artery could be identified. Furthermore, the base of the dog's heart is relatively inaccessible and the traction and rotation necessary to give good exposure often caused marked changes in the heart's rhythm.

After the experiment, the heart was allowed to drop back into the chest cavity and the pericardium closed with one or two sutures. The chest wall was closed by sutures passed directly through the cut ends of the costal cartilages and by tissue sutures. The subcutaneous tissues and skin were closed with silk or catgut and no bandages applied.

From ½ to 1 cc. of a 1 to 100 or 1 to 10 suspension of lycopodium spores in normal salt solution was injected—usually into the anterior descending branch of the left coronary artery, the vessel and its branches often being completely outlined as gray-white branches when completely filled with the suspension. After each step of the experiment and at varying intervals after the injection electrocardiograms were made—daily for a time after the operation and then usually weekly in dogs surviving for several months. At the time of death, either spontaneous or when the animal was killed, the heart was removed and studied grossly and microscopically, sections being made of all suspicious looking areas.

While some injections were made quickly and easily, others were extremely difficult and nearly impossible. This we felt was due to the small caliber of the vessels and the difficulty of introducing the needle into the vessel lumen, particularly during the rapid and at times violent contraction and movements of the heart. In general, it should be said that the entire technic is fairly difficult, particularly that portion associated with the actual injection.

III. **Results.** We shall discuss here the general results under a number of separate headings rather than to describe each experiment separately, (the details of which may be studied by those interested in the appended protocols). Of the twelve dogs operated on, five died before any attempt at coronary injection was possible—the result of the narcosis, operative trauma, hemorrhage, and so forth. Of the seven dogs actually injected, two died almost immediately following the injection, one died within 24 hours after the injection and four lived for a variable period after the injection—a period varying from two to three months. In all, 74 electrocardiographic curves were taken on the twelve animals.

(*a*) The Normal Electrocardiogram and the Effect of Morphin on the Dog's Heart. The electrocardiogram of the normal dog's heart differs in no essential particulars from that of the human heart. Einthoven[4] originally called attention to the high *R* wave in Lead II and the relatively lower and equal height of all waves in Lead I. In most of our dogs the *R* wave was high in all leads although highest in Lead II. Fig. 1 shows a typical dog's heart curve under the conditions of the experiment with the dog strapped in the dorsal position to the operating board, without morphin or anesthesia of any kind. The rapid rate, 135, and the peripheral muscle tremors are easily distinguished as well as the variation in rhythm—sinus arrhythmia.

It was noted quite regularly following the subcutaneous injection of ½ gr. morphin that the heart rate became markedly slower. Electrocardiograms taken during this relative bradycardia show the rate had dropped to 50 or 60 beats per minute with a slight increase in the *P–R* interval and a noticeable heightening of *T* specially in the second and third leads (Fig. 2). It is likely that

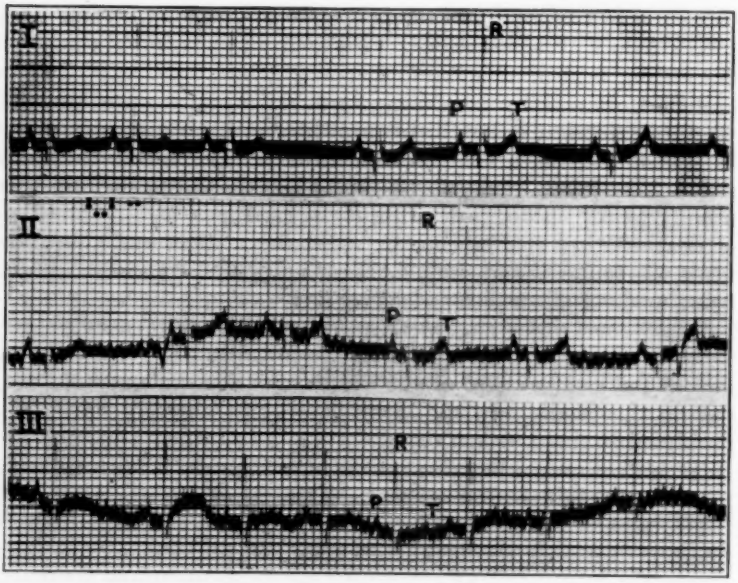

FIG. 1.—Normal curve. No morphin or anesthesia. Sinus arrhythmia. *P–R*, 0.10 second; rate, 135. Leads II and III show skeletal muscle tremors.

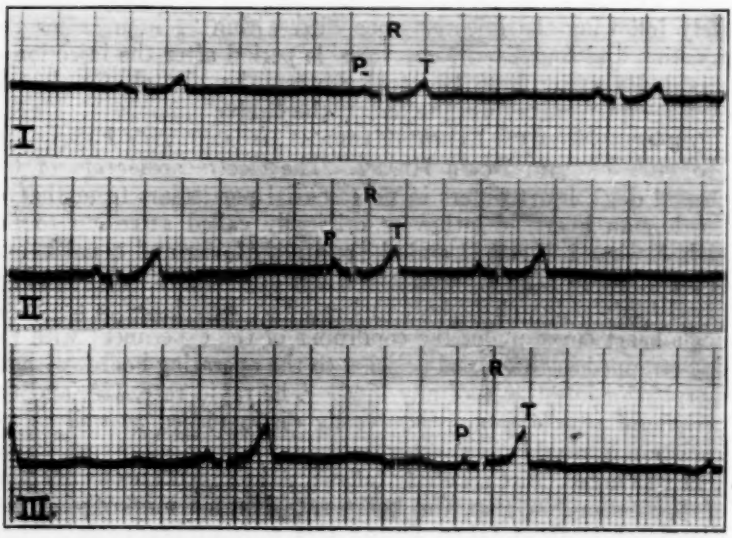

FIG. 2.—Bradycardia following injection of ¼ gr. of morphin. No ether. Sinus arrhythmia. *P–R*, 0.12 second; rate, 60.

central vagus stimulation is responsible for these changes due to morphin, as described by Cohn,[2] Einthoven and Wieringer[5] and von Brücke.[1] Cohn concluded that "morphin when injected intravenously into dogs causes a disordered rhythm resulting from its action on the cardio-inhibitory center. The arrhythmia exhibits characteristics of both right and left vagus stimulation and combinations of the two."

(*b*) The Effect of Ether Narcosis on the Dog's Heart. Although considerable experimental electrocardiographic research has been done on the dog's heart and the literature contains many references to the effects of chloroform anesthesia, we have been unable to find much work on the effect of ether anesthesia on the dog's heart. As a routine in our work we took electrocardiograms immediately following complete ether anesthesia and have found a number of interesting and suggestive results. Rather regularly in all animals the heart rate increased markedly from the relative morphin bradycardia before anesthesia of 50 or 60 to a rate of 120, 130, and so forth. Not infrequently with this tachycardia the *P–R* interval was prolonged from a pre-anesthesia reading of 0.12 to 0.14 seconds to 0.18 to 0.24 seconds. In five dogs (Nos. 1, 3, 5, 6, 7) a noticeable change in the direction or height of the *T* wave was found—either an inversion, a lowered or diphasic *T* wave, or a reversal of the pre-anesthetic direction. Increase in the height of the *T* wave was noted in one dog (No. 10); no change was observed in one (No. 4) and in five dogs no data on the effects of ether was available (Nos. 2, 8, 9, 10*a*, 10*b*). A typical ether effect may be seen in Fig. 3 (dog 3) showing an inversion of *T* in all leads, prolongation of *P–R* to 0.18 to 0.24 seconds, and a tachycardia of 125. The exact significance of these findings following ether anesthesia is not clear. However, they are of considerable importance in this research in view of the effects on the *T* wave following coronary injection to be discussed later. The inversion of *T* due to ether is neither as deep nor as peaked as the initial inversion due to coronary embolus, but resembles quite closely the subsequent or secondary inversions. A more intensive experimental study of the effects of ether narcosis would seem indicated from these results.

(*c*) The Effects of the Injection of a Suspension of Lycopodium Spores into the Coronary Circulation (Experimental Coronary Embolism). The results of lycopodium spore injections into the coronary vessels may be discussed under the following divisions, the immediate results without death of the animal; the immediate results with immediate death or death within 24 hours; the later results with the dog living over 24 hours to 6 weeks, 3 months and longer.

In the first group in which the injection of the lycopodium suspension was not followed by immediate exitus of the animal, a number of bizarre and curious phenomena were observed electro-

cardiographically, showing a complete inversion of the initial ventricular complexes in all leads with occasional ventricular extrasystoles immediately following the injection of ½ cc. of 1 to 100 suspension of spores into the anterior descending branch of the

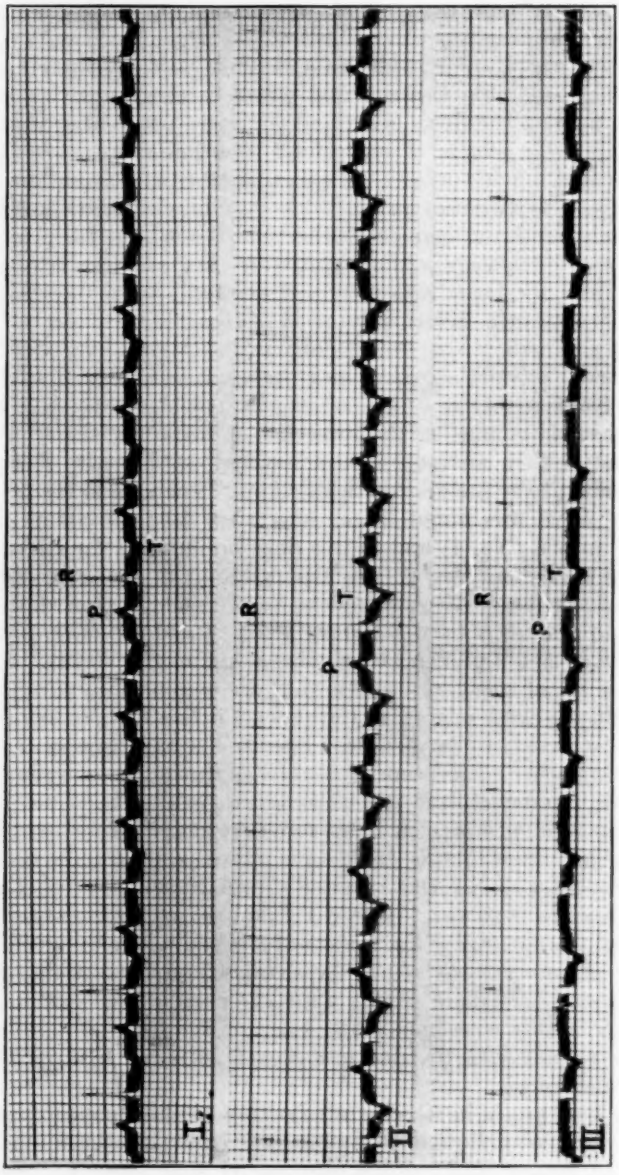

FIG. 3.—Effects of ether anesthesia. Inversion of *T* in all leads. *P–R*, 0.18 to 0.24 second. Before anesthesia *P–R* was 0.14 second; rate, 125.

left coronary artery. The T wave shows no inversion but is markedly elevated. P–R is reduced to 0.08 seconds. Twenty minutes later, a second injection was followed by a drop in the heart rate from 166 to 92, the presence of both upright and inverted initial complexes with right and left ventricular extrasystoles. The transitory character of these immediate effects following injection may be judged from the fact that a curve made four and a half hours later showed practically complete disappearance of all of these abnormalities with a restoration of the normal curve as found before the experiment was started—a slight inversion of T_1 being the only abnormality. Autopsy of this dog some weeks later disclosed several small areas of epicardial thickening, no endocardial lesions. Embedded in the ventricular musculature was an area about 1 mm. in diameter composed of young, partly differentiated connective tissue, surrounded by a thin layer of denser fibrillated connective tissue, outside of which can be seen a zone containing numerous fat vacuoles with a few compressed remnants of muscle fibers.

In the second group, where death occurred within a few minutes following the injection or within the first 24 hours, still more striking and bizarre curves were obtained. In dog No. 2, following the injection of 1.25 cc. of a 1 to 10 suspension, the descending branch of left coronary vessel stood out completely filled as elevated white outlined branches. Within 10 minutes the pulse was imperceptible and death occurred in 30 minutes. The electrocardiogram showed immediately after injection complete A–V dissociation with an abnormal rapid idioventricular rhythm and a curious obliteration of R–T interval (Fig. 4). Smith[18] mentions a similar fusion of R and T waves following the injection of bichlorid of mercury and nitric acid into the region of the apex and Eppinger and Rothberger,[6] describe somewhat similar curves following the injection of sublimate or silver nitrate into the deeper layers of the left ventricle as well as following incisions into the left ventricle with severing of the branch of the bundle.*

In dog No. 3, in which 0.5 cc. of suspension was injected into the right coronary vessel, death occurred toward the end of the first 24 hours, while immediately afterward a severe tachycardia due to auricular flutter with a 2 to 1 ventricular response with short periods of ventricular tachycardia may be identified.

Considering now the third group where the dogs survived over 24 hours and from then on to 10 weeks and over we may divide these late results of coronary injection into 3 subgroups: (*a*) The results in 24 to 48 hours; (*b*) the results from the fourth to eighth

* Oppenheimer and Rothschild describe a similar fusion of the ventricular components R and T in the acute stage of myocardial damage from coronary artery closure. B. S. Oppenheimer and M. A. Rothschild, The Value of the Electrocardiogram in the Diagnosis and Prognosis of Myocardial Disease, Trans. Assn. Am. Phys., 1924, **39**, 247. Krumbhaar found this also when intraventricular pressure was increased by partially clamping aorta or pulmonary artery (unpublished).

day after injection, and (*c*) the results from two to six weeks following injection. In dog No. 4 the curve immediately after injection showed a marked right preponderance. A curve taken 20 minutes later showed high-peaked *P* and *T* waves in Leads II and III with a tachycardia of 225. Within 48 hours after injection deeply inverted *T* waves in Leads II and III may be seen (Fig. 5), similar to those obtained by Smith following ligation. Within eight days this marked inversion of *T* was replaced by upright waves in all leads, arising prematurely from *R* in Lead II and

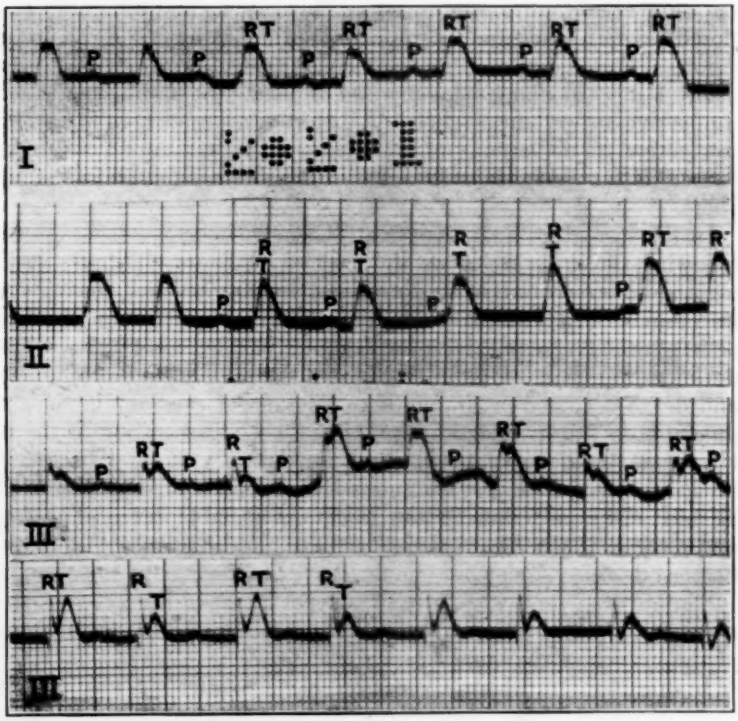

FIG. 4.—Dog No. 2. Immediately after injecting 1.25 cc. lycopodium. Complete *A–V* dissociation, auricular rate 115. Ventricular rate 135. *T* superimposed upon *Q–R–S* complex in Leads I and II, gradually emerging in Lead II.

bifurcate in Lead III. In 24 days, a right preponderance with inversion of T_1 was noted and in 57 days a secondary inversion of T_2 and T_3. Seventy-one days after injection *T* was found inverted in all leads but less deep and peaked than the inversion immediately following the injection (Fig. 6). The following day the dog was killed with chloroform, autopsy revealing an apical infarct with focal atrophy of the myocardium due to lycopodium spores (Figs. 7 and 8).

The relatively insignificant disturbance of the cardiac mechanism of dog No. 4 contrasts strikingly with the profound disturbance found in dog No. 5. Immediately following the injection of 2 cc. lycopodium suspension the beginning of Lead I shows a short period of comparatively normal mechanism followed quickly by a period of right bundle branch block interrupted by short periods of auricular fibrillation and flutter. Lead II shows periods of normal mechanism interrupted by periods of ventricular tachycardia and groups of

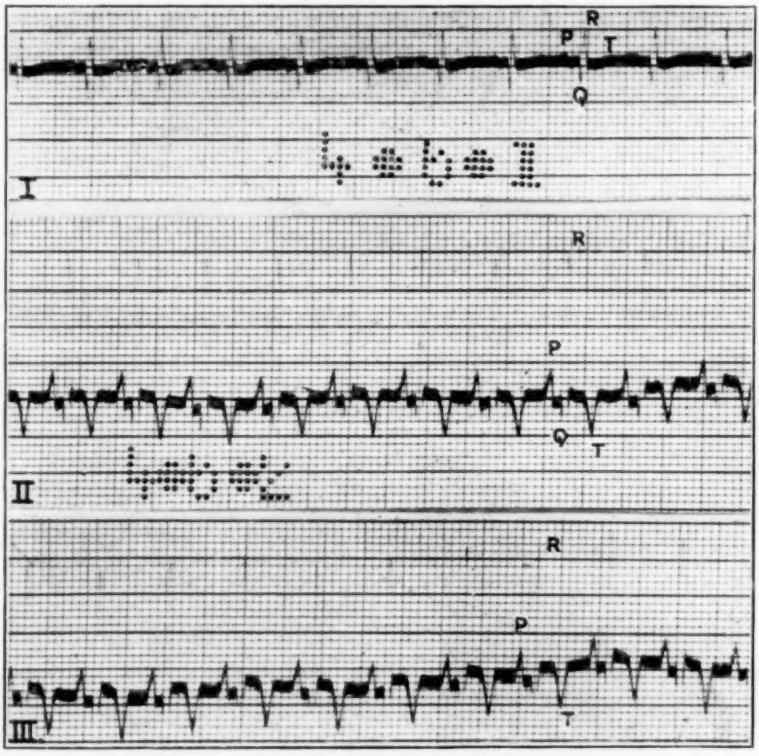

FIG. 5.—Dog No. 4. Forty-eight hours after injection. *T* deeply inverted in Leads II and III. *P* abnormally high in II and III. *P–R*, 0.08; rate, 165.

ventricular extrasystoles arising in or near the *A–V* node. This later focus finally dominated the mechanism. Lead III shows fairly normal mechanism interrupted by extrasystoles arising in or near the *A–V* node.

Twenty minutes after injection one finds an essentially normal mechanism. Within 24 hours deep inversion of *T* in all leads was found. Seventeen days after injection inversion of T_1 still persisted (Fig. 9). From then on, on various occasions (curves taken weekly

for six weeks), return to upright T waves with secondary and tertiary inversion of T in various leads occurred until the seventy-third day when the dog was killed. Autopsy revealed the myocardium and endocardium of the left ventricular surface of the apex and interventricular septum markedly fibrosed while microscopically a chronic interstitial myocarditis of the apical portion due to occlusion of arteries by lycopodium spores was found (Fig. 10).

FIG. 6.—Dog No. 4. Seventy-one days after injection. Right ventricular preponderance. Inversion of T in all leads. Apparent migration of pacemaker, with occasional block between origin of stimulus and auricular conduction system. P–R, 0.08 to 0.12 second; rate, 105.

Although dog No. 7 failed to show any striking changes immediately following injection, the curve taken 24 hours later showed the typical deep-peaked inversion of T referred to previously. Four and again eight days later T became upright only to again undergo a secondary inversion on the forty-third day (Fig. 11), at this time much less pronounced than the primary inversion. Autopsy revealed many recent subendocardial hemorrhages as well as some white scarring of the endocardium of the left ventricle. Microscopically beneath the endocardium and more deeply within the myocardium of the apex of the heart where the small pale areas

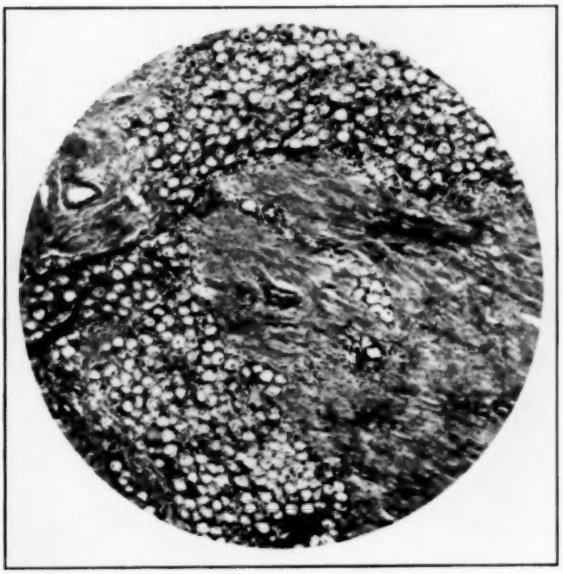

FIG. 7, Dog 4.—Apical infarct with focal atrophy of the myocardium with areas of closely packed lycopodium spores. EKG. showed primary and secondary inversion of *T* in all leads (Figs. 5 and 6).

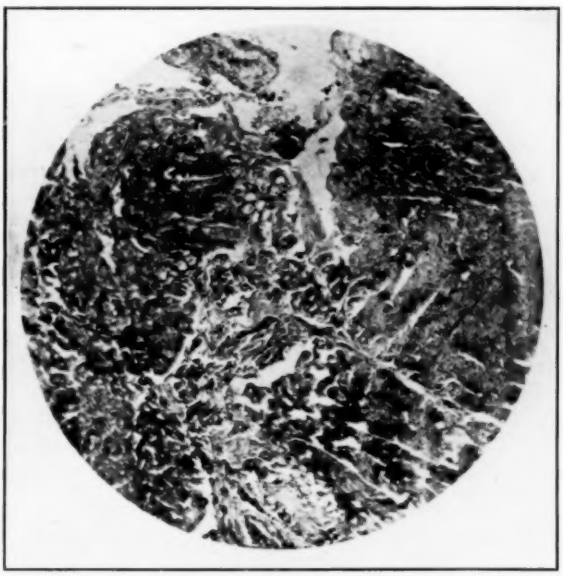

FIG. 8, Dog 4.—Myocardial degeneration with small number of lycopodium spores.

FIG. 10, Dog 5.—Chronic interstitial myocarditis (myocardium being replaced by broad bands of fibrous tissue) following occlusion of arteries by lycopodium spores. Note vessels filled with spores. EKG. showed primary and secondary inversion of *T* in all leads.

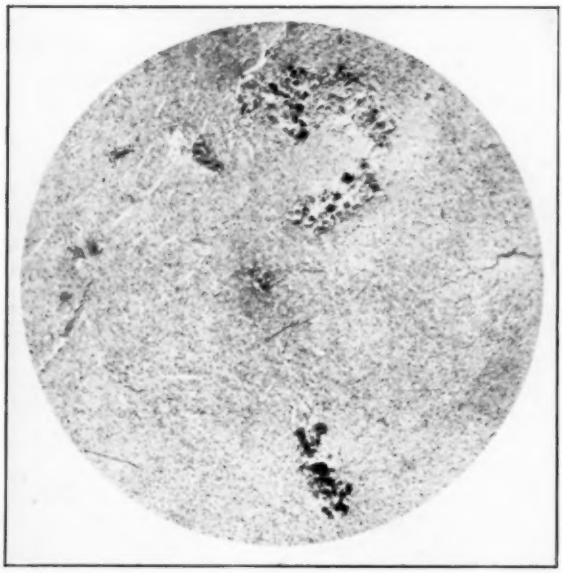

FIG. 12, Dog 7.—Areas of necrotic muscle fibers (focal necrosis) and calcification of myocardium. EKG. showed primary and secondary inversion of *T* (Fig. 11).

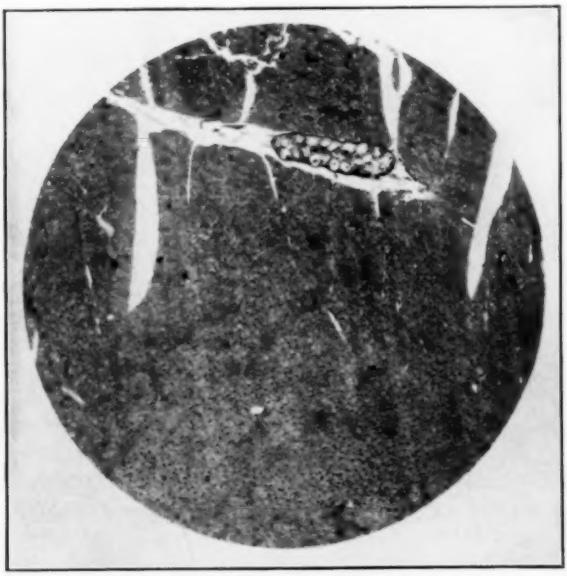

FIG. 13, Dog 10.—Acute cloudy swelling and fragmentation of heart muscle. EKG. showed ventricular fibrillation.

were visible in the gross, were numerous small areas composed of necrotic muscle fibers which stain deep blue because of calcium infiltration (Fig. 12). No lycopodium spores are visible.

One dog, No. 10, dying almost immediately following the injection from ventricular fibrillation, we wish to mention briefly. Following the injection into the anterior descending branch of the left coronary artery, the heart went into immediate fibrillation and within a few minutes the animal was dead. Autopsy showed a dilated heart with arteries pale, veins distended. Microscopic examination showed acute cloudy swelling and fragmentation of the heart muscle with congestion of myocardial vessels and many vessels packed with spores (Fig. 13).

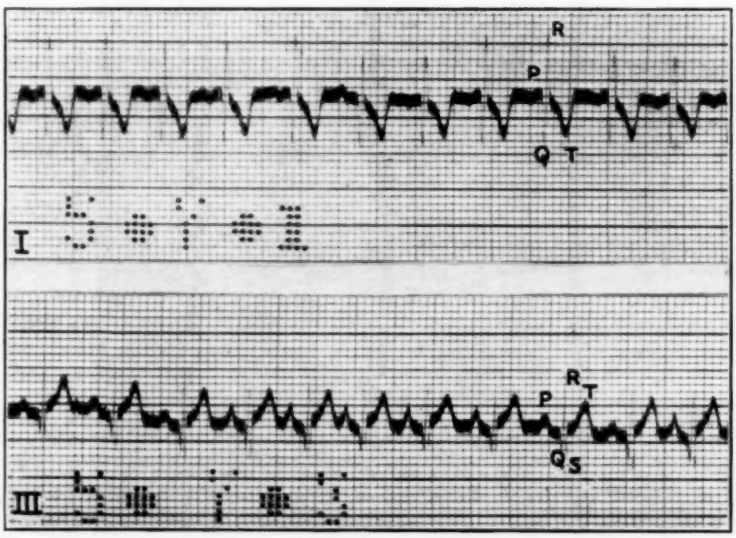

FIG. 9.—Dog No. 5. Seventeen days after injection. Inversion of *T* in I. Migration of pacemaker suggested by differences in *P*. *P–R*, 0.12 second; rate, 135.

IV. **Discussion.** Morphin administered hypodermically to dogs in ½-gr. doses causes a marked slowing (bradycardia) to a rate of 50 or 60 heart beats per minute. This slowing is probably due to central stimulation of the cardioinhibitory center as described by Einthoven and Wieringer, Cohn and others.

Ether narcosis in dogs causes quite regularly an inversion, decrease in height, diphasic contour, or change in the previous direction of the *T* wave of the electrocardiogram. It likewise increases markedly the heart rate from the morphin bradycardia of 60 before narcosis to a tachycardia of 120 to 130, meanwhile prolonging the *P–R*

interval to 0.18 to 0.24 seconds. The explanation of these effects from ether is not clear but suggests the need of further experimental work.

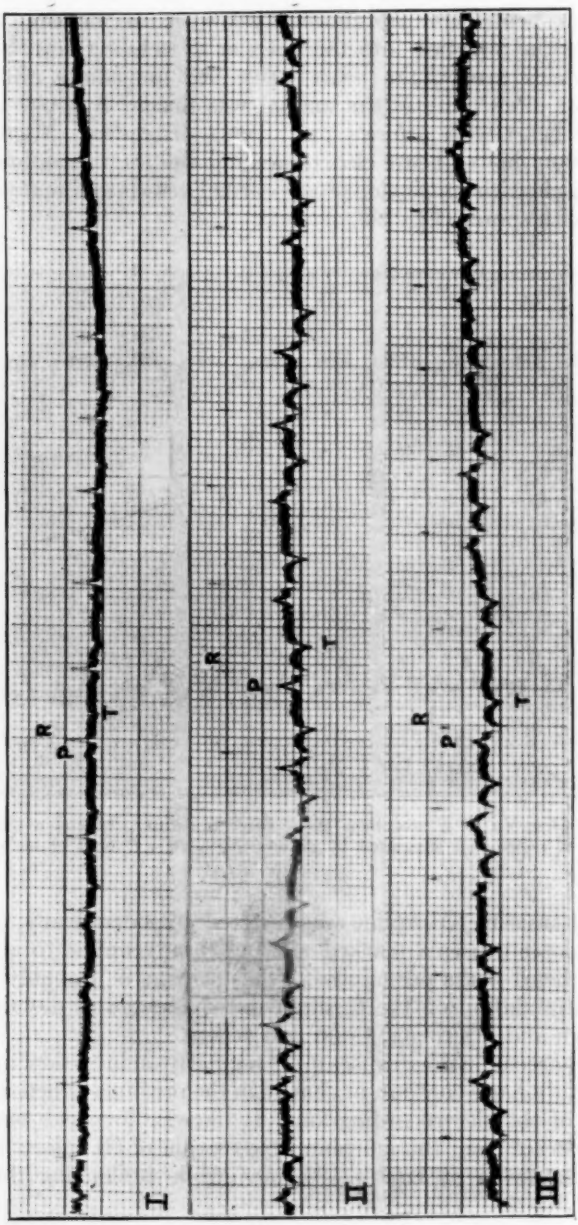

FIG. 11.—Dog No. 7. Forty-three days after injection. Inversion of *T* in all leads. *P–R*, 0.10 second; rate, 135.

The results of the injection of a suspension of lycopodium spores in the coronary circulation (experimental coronary embolism) vary depending on the size and number of vessels obliterated, the size and physiologic importance of the resultant ischemic area, as well as the rapidity of the establishment of collateral circulation. Relatively widespread and sudden obliteration of arterioles and capillaries from massive lycopodium spore injections results in immediate death of the animal, the electrocardiogram showing complete *A–V* dissociation, obliteration of the *R–T* interval, auricular flutter or ventricular fibrillation. The injection of a smaller number of spores with the involvement of smaller areas of the heart is compatible with complete recovery of the animal, the electrocardiograms in such dogs showing variously, inversion of initial ventricular complexes, right ventricular preponderance, nodal rhythm, ventricular extrasystoles, with primary and secondary inversion of the *T* wave. The apical areas of the hearts of these dogs show typical chronic interstitial myocarditis scarcely to be distinguished from that occurring in man as a result of atherosclerotic obliteration of the smaller coronary vessels.

When the injections missed the lumen of the vessel to any considerable extent, no permanent change in the electrocardiogram (*T* wave) was found, although strange and curious findings were noted transitorily. At autopsy the lesions noticed were epicardial and not confined to the apex. It is probable that the slight hemorrhage and trauma incidental to the injection and manipulation of the heart must be held responsible for these transient bizarre phenomena.

When massive injections were followed promptly by death of the animal, ventricular fibrillation was found in the most sudden death, exitus occurring almost at once following the injection; the dog dying within 30 minutes showed complete *A–V* dissociation with obliteration of the *R T* interval, while the animal dying within the first 24 hours showed a severe tachycardia with auricular flutter.

In the dogs surviving for days and weeks following the injection the changes in the *T* wave are at once the most interesting and the most difficult to interpret. In most instances inversion of *T* did not occur immediately, curves taken 20 minutes after the injection showing a physiologic curve. Within 24 to 48 hours, however, all showed the deep-peaked inversion, which again about the eighth day became upright. From then on at varying intervals secondary and tertiary inversions and return to the upright position occurred, each inversion, however, being less pronounced and deep than the preceding. Quite regularly the dogs showing the most marked inversion showed at autopsy infarction in the apical region of the left ventricle. While much work and considerable difference of opinion exist as to the significance of the inversion of *T*, and while it is generally felt that *T* is a relatively labile wave, easily influenced

by many procedures and by lesions in various areas of the heart, this work lends support to the view that inversion of *T* is due to an area of infarction in the apical region of the left ventricle and that its direction is due to prolongation or delay of activity at the apex in relation to final activity at the base. Further, the degree and configuration of the inversion varies with the cause, witness the type of inversion due to ether with that following infarction. Assuming in the latter, that inversion is due to structural changes at the apex, it is difficult to understand the changes in direction from day to day and week to week, tempting one to speculate on the probable parallel changes in pathology as healing goes on from the possibly initial ischemia, cloudy swelling and fragmentation, to possibly secondary congestion, edema or hemorrhage, with inflammatory reaction and finally newly-formed connective tissue and fibrosis.

Conclusions. 1. Hypodermic administration of morphin to dogs causes marked bradycardia, probably due to central stimulation of the cardio-inhibitory center as described by Einthoven and Wieringer, Cohn and others.

2. Ether narcosis in dogs causes inversion and other changes in the *T* wave of the electrocardiogram, acceleration of the heart rate and prolongation of the *P–R* interval.

3. Injection of a suspension of lycopodium spores into the coronary circulation of dogs (experimental coronary embolism) causes:

(*a*) Death at once, or within 24 hours, depending on the amount of the injection and the size of the resulting infarct, the animals dying immediately, showing ventricular fibrillation; those dying within 30 minutes, complete *A–V* dissociation with obliteration of the *R–T* interval; those within 24 hours, tachycardia from auricular flutter, with cloudy swelling and fragmentation of the myocardium, and vessels distended with spores.

(*b*) Changes in the electrocardiogram compatible with life, such as inversion of initial complexes, right preponderance, nodal rhythm, ventricular extrasystoles, ventricular tachycardia.

(*c*) Primary, secondary and tertiary inversion of the *T* wave of dogs surviving the injection for two to three months, the heart at autopsy showing quite regularly infarction (fibrosis) of the apex of the left ventricle with vessels filled with spores, with typical chronic interstitial myocarditis scarcely to be distinguished from that occurring in man, the result of atherosclerotic obliteration of the smaller coronary vessels.

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SPONTANEOUS RUPTURE OF THE HEART.*

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Spontaneous rupture of the heart is regarded as of infrequent occurrence, and is seldom recorded in civil hospital records. In coroners' services and in institutions for the insane such instances are more frequently found. They are undoubtedly being missed in private hospital practice.

Numerous individual and collected reports of spontaneous rupture of the heart may be found, yet a comprehensive study of this subject is lacking in the English literature. We have gathered 320 instances from the literature and have added 5 from our own material, classifying the symptoms according to their incidence and giving particular attention to the etiology and pathology. We will show that this condition most frequently follows obstruction of a coronary artery. Coronary thrombosis invariably results in infarction of that portion of the heart wall supplied by the obstructed vessel. Proper management of such a patient will aid in preventing a rupture of the infarcted area.

Etiology. The age incidence and the more common predisposing factors resulting in spontaneous heart rupture in 245 instances in which the age was mentioned are given in Table I.

* A paper on this subject will also be found in this Journal, 1925, **170**, 828.

TABLE I.

Age.	Number.	Predisposing cause.
Birth to 10 years . . .	1 (aged 5 years)	Syphilitic myocarditis.[18]
10 to 30 " . . .	1 (aged 22 ")	Gumma of heart.[4]
30 to 50 " . . .	1 (aged 35 ")	Obliterative endarteritis of the coronary arteries.[6]
	2 (aged 30 " and 36 ")	Sclerosis of the coronary arteries and myomalacia cordis.[12,19]
	1 (aged 36 ")	Ulcerative endocarditis.[1]
	1 (aged 45 ")	Syphilitic myocarditis.[4]
50 to 60 " . . .	10	Myomalacia cordis.
60 and beyond . . .	209	Myomalacia cordis most frequently recorded.
80 to 90 years . . .	4	Myomalacia cordis.

The two sexes are nearly equally divided in Quain's review of 100 examples.[3] In 218 instances from our group, 122 were males and 96 females.

The common predisposing cause which was responsible for 226 of the 325 ruptures from which this study was made was an embolism, or an atheromatous sclerosis and thrombus formation in a coronary artery or arteries, resulting in an anemic infarct. The condition of the coronary arteries was not stated in 93 instances. Undoubtedly some of these would have presented changes, had they been looked for. Anemic infarct has been termed myomalacia cordis in many of the reported instances. Other unusual causes were, ulcerative endocarditis,[1, 2] abscess of the heart wall[3] and gumma of the heart wall.[4]

Exciting factors are not necessary. Mental strain, extreme emotion and physical exertion have been stated by some as present at the time of rupture. In our study, we found that more frequently there was no exciting factor and that rupture occurred while the patient was at rest.

A large proportion of the reported examples of heart rupture occurred in the insane. We have found no explanation of this. Since the usual cause is primarily arteriosclerosis, one might conjecture that the manner of living, sedentary habits and often irrational diet of insane patients predispose to arterial lesions. Statistics on the incidence of arteriosclerosis in the insane bear this out.

Pathology. Spontaneous heart rupture does not occur without lesion of the myocardium. The pathological changes may only be detected by microscopic study. Given a weakened heart wall, any condition which raises the blood pressure in such a chamber favors its rupture.[1] Stenosis of the tricuspid valves or obstruction in the pulmonary circulation favors rupture of the right heart. Aortic stenosis, mitral stenosis or increased arterial pressure favors a rupture of the left heart, and yet these are theoretical reasons since very few ruptured hearts present such valvular changes.

Sclerosis of the coronary arteries was found in a high percentage of instances in which rupture of the heart wall occurred.

The ruptures may be single or multiple, complete or incomplete, direct or indirect. They may vary in size from a few millimeters to 4 or 5 cm. They may be located in any area of the heart wall. Table II gives the anatomic locations.

TABLE II.

	Examples.
Anterior wall, 66 per cent Posterior wall 34 per cent	115
Left ventricle	253
Right ventricle	35
Right auricle	16
Left auricle	4
Interventricular septum	1

In unusual instances ruptures may be multiple. In 3 instances two separate ruptures were found.[1,5,6] In 2 other instances[7,8] one channel had an exit through two or three slits in the epicardium. In a recent autopsy in this hospital, three linear tears through the epicardium were located over a large healed infarct in the left ventricle.

The process of atherosclerosis of the coronary arteries, as of other arteries, consists first of a swelling of the intercellular cement substance in the intima. This is followed by a swelling of the intimal cells themselves, and a deposition of hyaline material resulting in a thickening of the intima. Lipoid substances from the blood stream are deposited in these areas in increasing amounts until an "asphyxiation necrosis" results.[10] This is followed by the formation of calcium soaps. By this time the endothelial lining of the intima has broken through and on the exposed atheromatous ulcer a thrombus forms which increases progressively in size until the narrowed lumen is entirely obliterated, depriving the distal heart muscle of its blood supply. An ischemic infarct in the heart muscle results.[9] Various names are given in the literature to this area of ischemic necrosis, for example, myomalacia cordis, coagulation necrosis, fatty degeneration and anemic infarct. Each of these is descriptive of some phase of the process of necrosis and all apply to the condition of ischemic infarct.

As soon as the blood supply of a given area of the heart wall becomes insufficient, degeneration of the heart muscle takes place. The cells become swollen, lose their striations and appear finely granular. They finally lose their cell outline and deep staining granules and pyknotic nuclei remain. In the degenerated cells are accumulated globules of fat so that the process is described by Quain as fatty degeneration. During this degenerative process, according to MacCallum, a ferment is produced which coagulates the intracellular and extracellular fluids so that a firm coagulum

is formed in this area.[11] Through phagocytic ferment action the coagulum is finally softened and absorbed. The heart wall becomes thinned and is weakened so that an aneurysm may result. The blood from the heart chamber forces its way through the softened heart muscle dissecting a ragged, irregularly-shaped channel. A cavity is thus produced within the heart wall which is filled with necrotic muscle tissue and clotted blood. Rupture finally occurs through a linear slit in the epicardium extending parallel to the long axis of the heart.

Gross Pathology. The heart is usually found to be hypertrophied, due to the fact that many instances are associated with hypertension and generalized arteriosclerosis. The cut surface of the myocardium is pale yellow in color with a greasy, glistening appearance. A colored zone of hemorrhagic infiltration into the necrotic muscle, 1 to 2 cm. in width, surrounds the rupture. There is a thinning of the wall in this region, which is soft and friable and punctures easily.

The pericardial sac is distended with 300 to 500 cc. of fluid and clotted blood. In an unusual instance the pericardium was adherent to the site of rupture and rupture took place into the mediastinum.[12] Instances are mentioned in which complete rupture was prevented by an adherent pericardium.

Microscopic Pathology. Each of our examples had an obliterative thrombosis of a coronary artery. Atheromatous degeneration was also found in the smaller branches, with resulting partial obliteration. Near the ruptured area the muscle cells presented various stages of degeneration. In some this was manifested only by a yellow-brown pigment surrounding the nuclei and by fading of the striations. In other areas, only small fragments of muscle cells remained. These had pyknotic nuclei, no striations, and were imbedded in a fibrous tissue network containing leukocytes and plasma cells. In all sections examined, wandering cells infiltrated the involved area and small areas of round-cell infiltration were seen. At the margin of the rupture an organized thrombus was attached to the necrotic heart muscle.

Myocarditis. All carefully studied instances of spontaneous heart rupture occurring under thirty years of age have been due to syphilitic myocarditis. Several instances of spontaneous rupture were mentioned in the literature in which no gross myocardial changes were evident. Inasmuch as syphilitic myocarditis may present no gross pathology, it seems plausible that a certain number of these instances, if studied microscopically, might come under this group.

Warthin has described certain pathognomonic microscopic characteristics in congenital syphilis of the myocardium.[13] The smaller arteries have a lymphocyte, plasma cell, collar infiltration. Proliferating interstitial fibroblasts and groups of large, pale

staining, irregular-sized endothelial cells and round cells are characteristic. Spirochetes, diffuse and numerous, may be found by special staining methods. There are areas of coagulation necrosis and fatty degeneration of the heart muscle in which no fibrosis or spirochetes are found. Some of the smaller vessels show endothelial cells proliferating in their walls after filling the lumen. The adventitia undergoes fibrous thickening and the perivascular tissues present fibrous hyperplasia and lymphocyte and plasma-cell infiltration. The interstitial changes are more marked than the vascular changes.

St. George[4] briefly describes a rupture due to a gumma of the anterior wall of the left ventricle. No other instance was found in the literature. We have not been able to find an instance of echinococcus cyst or tumor of the heart wall causing rupture. These were mentioned frequently in the literature as predisposing causes.

Symptomatology. In our study of 325 examples of ruptured heart wall, less than 25 per cent gave a history suggesting previous heart disease. These fell into one of two groups: The larger group gave a history of dyspnea and rapid heart action on exertion, cyanosis and varying degrees of precordial distress, which varied from mild precordial discomfort, leaving promptly upon the cessation of exertion, to severe attacks of pain with radiations characteristic of angina.

The second, and smaller group gave a history of symptoms referable to disturbances below the diaphragm, often gastric in nature. Epigastric pain was most often noted.[14] This pain had no relation to the ingestion of food and was not relieved by vomiting when vomiting did occur. The pain usually persisted in the upper part of the abdomen. Radiation to the right or left subscapular region was noted frequently. Radiation to the right subscapular region, together with epigastric tenderness and vomiting, occasionally led to the diagnosis of gall bladder disease.

Approximately 75 per cent of the instances of ruptured heart wall gave no history suggesting heart disease previous to the time of final illness. These patients fell again into two groups: In only a comparatively few instances was death without premonitory warning. These patients sustained sudden collapse, cyanosis and coma. The heart action and respirations stopped within one to two minutes.

A very large majority of patients lived from a few hours to two days after the onset of the final illness. In this group the most common symptom was a severe, persistent, tearing pain in the precordium or beneath the sternum. This pain, in an occasional patient, radiated down the left arm or into the neck. The skin was pale. Drops of perspiration stood out on the face and body. The pulse was usually rapid, often irregular, and became progressively weaker. In a few instances the pulse was slow. Many

patients had temperatures from 99° to 101°. From these symptoms, which were indicative of a desperate situation, the patient frequently rallied temporarily. Death usually followed suddenly within a few hours to two days in a manner previously described. References are made to one patient living eight days and one living seventeen days after rupture occurred.[15,16] From descriptions of the symptomatology and the pathologic processes in these instances, we believe this not to be the case. In these patients we believe that the primary symptoms were due to coronary thrombosis which in turn was followed by infarction of the myocardium. When rupture finally does occur, death ensues within a few minutes.

A careful survey of the histories of many of the reported instances of ruptured heart leads one to believe that acute coronary obstruction did occur. The primary symptoms were due to this accident. The processes of infarction in the area in which nutrition was interfered with through obstruction to its arterial supply of blood, resulted in a marked weakening of the heart wall, through which the blood forced its way.

The physical findings, either at the time of acute coronary obstruction or at the time of rupture, may be negative. The heart may dilate. A pericardial friction rub may develop. Cardiac irregularities occur, due to auricular fibrillation, extrasystoles or heart block (an observation by Dr. Herrick). The heart sounds thus become faint even before rupture occurs.[31] In one instance the murmur caused by the passage of blood through the ruptured heart wall was heard and a clinical diagnosis of this condition made.[33] This was corroborated by necropsy. The increase in size of the pericardial sac as it becomes filled with blood may be detected by the extension of dulness to the left beyond the nipple line.

Diagnosis. The diagnosis of rupture of the heart wall resolves itself into a primary diagnosis of obstruction of a coronary artery, of which we found clinical or pathological evidence in 226 of the 325 instances making up this study.

The recognition of coronary obstruction has been materially aided as the result of a paper published by Dr. J. B. Herrick[17] in 1919 in which the clinical features were carefully discussed. His classification of this condition outlined three groups: (1) Instances of sudden death; (2) instances of death within a few minutes to a few hours; (3) instances in which death was delayed to days or weeks. The material from which our study was made fits equally well into this classification, as it should, since much of it has the same pathologic basis.

The statement has frequently been made that rupture of the heart can only be ascertained by autopsy. In this connection Dr. Herrick's discussion of acute coronary obstruction is apropos: "As in so many other conditions, the first essential is to think of this condition as a possibility and to rid the mind of the notion that

such a diagnosis is possible only at necropsy." The first step will then be to diagnose coronary obstruction. Having made this diagnosis, rupture of the heart wall through the infarcted area becomes a matter of prognosis if the patient still lives, and a possibility to have in mind if the patient dies suddenly.

Treatment. The early recognition of acute coronary obstruction is of vital importance, since it permits of measures that may prevent rupture of the area of infarction. The pain should be controlled by adequate doses of morphin, hypodermically. Since increased energy of the heart favors rupture, it is better to avoid cardiac stimulation by drugs. Absolute rest in bed for a long period of time should be insisted upon to allow healing of the infarct. After rupture has occurred, death follows so quickly that treatment cannot be instituted. Suture of the rupture has been suggested, but must be an impossible procedure because of immediate collapse.

Examples. Our first example is an instance of thrombosis of the coronary artery occurring twenty-four hours before death. Rupture of the infarct undoubtedly occurred at about the time of admission to the hospital.

F. H., a white male aged seventy-four years, was admitted to the Santa Barbara Cottage Hospital in collapse. He was extremely cyanotic. The extremities were cold. The respirations were of the Cheyne-Stokes type. The pulse was imperceptible. He died within ten minutes.

Twenty-four hours before, he had consulted a physician on account of sudden precordial distress, great weakness, dizziness and rapid heart action. The physician had advised him to go to bed. This he did, but arose early the next morning and started in his automobile for a destination 100 miles distant. His precordial distress increased in severity and an hour before admission to the hospital he was forced to turn the wheel over to a companion who drove him to the hospital. He is said to have suffered excruciating pain in the chest during this last hour.

Postmortem examination revealed a pericardial sac distended with clotted blood. On the posterior surface of the left ventricle, 4 cm. from the septal line and 6 cm. from the apex, was a linear tear in the heart muscle, 2 mm. in length, through which a probe could be passed into the ventricular cavity. The muscle tissue surrounding the aperture—an area 3.5 cm. in diameter, was soft, friable, dark in color and infiltrated with blood. The inner aperture was covered by an organized blood clot. The aorta, aortic valves, orifices of the coronary arteries and intima of the coronary arteries were markedly sclerotic. The left branch of the anterior coronary artery was completely occluded 2 cm. above the site of rupture by a thrombus. The heart weighed 380 gm. The muscle of the left ventricle measured 2.5 cm. in thickness. All other valves than the aortic were normal.

Our second example is one of rupture of the heart occurring without premonitory symptoms having been noted.

Mr. Charles S., a private patient of Dr. H. O. Koefod, had suffered from gout for forty years. He was eighty-four years of age. For several weeks prior to death he was bedridden. During this period the pulse was normal in rate, character and regularity. The radial arteries were markedly sclerotic. The blood pressure was systolic, 140; diastolic, 90. The patient had had no symptoms referable directly to the heart. After a half hour's absence the nurse returned and found him dead.

Postmortem examination revealed a hemopericardium. There was a linear tear through the myocardium of the left ventricle at the apex. The tissue surrounding the aperture was necrotic and measured only 2 mm. in thickness. Surrounding the inner aperture was an organized blood clot. The cause of the infarct was a thrombus in the anterior coronary artery 1 cm. above the site of rupture. The aorta, aortic valves and coronary arteries were sclerotic. The muscle of the left ventricle measured 2 cm. in thickness. The heart weighed 400 gm.

Our third example is again of the type in which premonitory symptoms were not noted.

Mrs. M. A., an elderly white woman, was admitted to the White Memorial Hospital, in Los Angeles, on February 14, 1924. She had a hypertension, her pressure being: systolic, 220; diastolic, 130. The left border of the heart was 1 cm. beyond the nipple line. The urine contained a trace of albumin and sugar. The blood sugar was 0.23 per cent. She did not complain of any symptoms referable to heart disease. On February 21 the patient complained of pain and a sense of fullness in the epigastrium. On February 22 she again complained of this fullness, which was relieved by soda. On February 23 the patient felt well. At 3 P.M. she went to the bathroom and returned to bed, making no complaint. At 6 P.M. she was found dead in bed with no evidence of a struggle.

Postmortem examination revealed a pericardial sac distended with blood. A tear 1 cm. in length was found through the anterior wall of the right ventricle, close to its apex. The muscle surrounding the tear was infiltrated with blood for a distance of 1.5 cm. surrounding the rupture. The aorta and aortic valves were sclerotic. The condition of the coronary arteries was not stated. The muscle of the left ventricle was increased in thickness.

Our fourth example illustrates a thrombosis occurring seven days before rupture of the heart wall.

Mr. S., aged sixty-eight years, was a private patient of Dr. L. W. Hotchkiss in the Santa Barbara Cottage Hospital. He had undergone a prostatectomy and his surgical recovery was progressing uneventfully. He was suddenly seized with tearing precordial

pain. He broke into a perspiration, the pulse became rapid and weak. Within twenty-four hours a friction rub was audible over the precordium. Marked tenderness persisted over the entire precordium. On the seventh day following the onset of this precordial disturbance, the patient complained again of agonizing pain about the left nipple and was dead within one minute's time.

Postmortem examination revealed a linear longitudinal tear in the anterior wall of the left ventricle 2 cm. in length, situated 1 cm. from the septum and 6 cm. from the apex. Surrounding the aperture was an area of necrotic muscle 3 cm. in diameter. This necrotic area was 5 mm. in thickness. The right branch of the anterior coronary artery was completely occluded by a thrombus. There was present only a moderate sclerosis of the root of the aorta and of the aortic valves. The coronary arteries presented a more advanced degree of sclerosis. The muscle of the left ventricle was 1.5 cm. in thickness. The heart weighed 270 gm. No other abnormality was seen.

Our fifth example is a specimen obtained from Dr. A. M. Moody of San Francisco. The clinical history of this patient was not available.

Examination of the heart revealed a linear longitudinal tear 1 cm. in length in the posterior wall of the left ventricle 3 cm. from the septum and 5 cm. from the apex. The external aperture opened into a cavity 1.5 cm. in diameter surrounded by an organized blood clot and necrotic muscle. The inner aperture was circular and measured 1.5 cm. in diameter. Surrounding the aperture was an area of necrotic muscle 1 to 2 cm. in width; 2 cm. above the site of rupture the posterior coronary artery was occluded by a thrombus. The root of the aorta, the aortic valves and the coronary arteries were markedly sclerotic. The muscle of the left ventricle measured 2.3 cm. in thickness. The heart weighed 340 gm. No other abnormality was seen.

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SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD AND PERNICIOUS ANEMIA.

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Pernicious anemia, as a clinical entity, was described by Addison in 1855 and by Biermer in 1868 with a lucidity which has never been excelled. While Addison called it idiopathic, Biermer gave

it the name pernicious anemia. H. C. Wood, Cohnheim, Minnich and others developed our knowledge in regard to the pathogenesis of the bone-marrow lesions and the changes in the blood film. The clinical picture, lemon-tinted skin, whitish mucous membranes, Hunter's glossopharyngitis, gastric achylia, diarrhea or constipation, is well known and needs no further comment. The blood film with its anisocytosis, poikilocytosis, decreased platelets, its embryonal cells such as megaloblasts, and the abnormal color index over 1, as well as the icteric index (J. Evans) of the blood serum over 11 and the bile pigments; urobilin and urobilinogen in the duodenal juice demonstrate further the increased hemolytic activity. This hemolytic activity may perhaps be produced by a primary auto-intoxication (Naegeli) or by a hypothetic poison of the intestinal tract (Hunter, Morawitz, Eppinger, Hurst and Bell). Each theory of etiology of hemolytic activity has its followers and its adversaries, and has given rise to many and widely diversed methods of treatments. Limit of space prohibits the discussion of these theories and the relative merits of these therapeutical measures. We incline to accept the gastrointestinal genesis of pernicious anemia and believe that toxins of the intestinal tract pass through the constitutionally changed walls of the intestines. They must be of hemolytic and neurotoxic nature and produce more or less severe damages in the bone marrow or nervous system. It is then easy to understand that according to the prevalence of the toxic action clinical and neurologic pictures are to be found.

Spinal cord lesions were studied in pernicious anemia at first by Noone, who demonstrated such anemic cord lesions in histologic sections. They are formed by small sclerotic lesions beginning around the bloodvessels, producing secondary ascending and descending tract degenerations in the posterior or posterolateral tracts of the white matter. Dana and Putnam in 1891 and Russell, Batten and Collier described a series of cases in which the nervous symptoms of posterolateral tract lesions precede the anemia and state that between Nonne's findings all kinds of different stages occur. They called these pathologic lesions subacute combined degenerations of the cord. Newer investigations of these cord degenerations in pernicious anemia have been made by Henneberg and Wohlwill in Germany and by Williams and Grinker in America. Henneberg called the neurologic picture myelitis funicularis, but later changed this term to myelosis, demonstrating that these primary degenerations are without inflammatory infiltrations in the cord. That such subacute degenerations also involve the gray and white matter of the brain has been shown by Woltman and Troemmer. As already mentioned, the subacute combined degenerations affect only the white matter and more especially the posterior than the lateral tracts, beginning at first in the medial area (Burdach) of the cervical cord and gradually descending below

to the sacral region and ascending into the medulla oblongata and brain. Degenerations have never been observed in the gray matter of the cord or in the extra or intramedullary roots. The histologic picture shows: (1) Granulation and destruction of the myelin sheets of the axis cylinder; (2) neurolytic swelling of the axis cylinder (boules terminales), and (3) secondary tract degeneration.

The degree of the nervous disorder is not always parallel with the severity of the blood disease. If the latter is severe, the course is usually rapid, thus giving no time for the development of changes in the spinal cord and only a few of the focal lesions are to be seen. If on the other hand subacute combined degenerations are numerous, we also find multiple tract degenerations and the blood picture of the preanemic stage. As to the relationship between the development of the blood changes and the onset of neurologic symptoms, there is no constancy whatever. We differentiate our clinical and neurologic pictures as follows: (1) Pernicious anemia without symptoms of involvement of the spinal cord; (2) pernicious anemia with slight signs of spinal cord lesions; (3) pernicious anemia with the typical picture of myelosis. (4) myelosis with the preanemic stage; (5) myelosis without anemia.

The typical neurologic signs are often preceded by subjective complaints, such as weakness, fatigue, numbness, pricking sensation in legs and arms, soreness of tongue, headaches, dizziness, fainting spells, insomnia, depression and delusions, and even hallucinations. Examination reveals the clinical signs: Slightly dilated pupils with sometimes retinal hemorrhages; exaggerated or decreased tendon reflexes, Babinski's sign and cloni; spastic-paretic gait; diminution or loss of the vibratory senses; ataxia and rarely choreoathetotic movements. The sensory findings vary from anesthesia to hyperesthesia or hyperalgesia and are often changeable dependent on the surrounding temperature. Real shooting neurotic pains are often present, and in, at least, 4.9 per cent of cases multiple peripheral neuritis is to be found. The slight muscle atrophy shows quantitative decreased electric irritability. Due to the atrophy of the tongue, the speech is involved and simulates the speech seen in multiple sclerosis. Naturally multiple sclerosis, with its classical picture, makes no difficulty in diagnosis and can easily be eliminated.

As already stated, the blood film does not go hand-in-hand with the clinical findings of spinal cord involvement. Therefore, the diagnosis of myelosis or subacute combined spinal cord lesions without the blood changes of pernicious anemia should be made.

We present histories of cases which in their findings are characteristic for cord lesions, though the blood film would give cause for differences of opinion. These few histories show that in all cases the vibratory sense is disturbed. We wish to call special attention to this neurologic symptom as the earliest objective finding in involvement of the posterior roots. Diminution or loss of the vibra-

tory sense is easily tested for and, if found, cautions us to suspect further development of subacute combined degeneration, even without the blood findings of pernicious anemia.

In regard to treatment, we use blood transfusion, arsenicals and hydrochloric acid with questionable results. In our opinion the therapy of pernicious anemia and of subacute combined degeneration of the nervous system should be taken from a different point of view. There is very probably a relationship between pernicious anemia and hypoadrenia (or Addison's disease), both showing skin pigmentation, adynamia, anemia and similar neurologic findings. We believe that further investigation will reveal the connection between the two clinical pictures.

Case Reports. CASE I.—C. R., an American laborer, aged twenty-nine years, was admitted to the hospital on January 19, 1925, complaining of weakness. He claims that he was in fairly good health until May, 1924, when he began to have soreness of his mouth and tongue and a peculiar taste in his mouth. In July, 1924, he first noted weakness and loss of strength, which gradually progressed until he was no longer able to work. At first, weakness involved only the lower extremities, but later the upper extremities as well became involved. He was transfused three times within a short period of time and after the last transfusion in October, 1924, the patient felt fairly well for about six weeks. In December, 1924, he contracted a severe cold and the old symptoms returned. At this time his legs became numb and the feet, ankles, hands and face became swollen. Several weeks before admission he developed a productive cough, especially in the morning bringing up tenacious purulent sputum in small quantities. The appetite has been exceedingly poor since the onset of the present illness and he has always been constipated. The past medical and family histories are essentially unimportant.

On physical examination it was noted that the patient was well developed but undernourished, with a pasty lemon-yellow color to the skin throughout the body. His speech was slurring in type and at times very difficult to understand. Examination of eyes revealed unequal pupils, the right being larger than left, but both reacting to light and distance. Both bulbar and palpebral conjunctivæ were pale and icteric. The mouth showed marked paleness of the mucous membrane. The tongue was smooth. The neck showed definite visible pulsations and a continuous thrill over the right jugular bulb, which was greatly accentuated with expiration and almost lost on inspiration, and a bilateral systolic bruit. Examination of the chest showed definite infiltration of right apex with coarse leathery friction sounds at the base of right axilla and a fine pleural click at the height of inspiration and the end of expiration at the right scapular spine. The heart showed some enlargement both to the right and left of the sternum, with a systolic murmur heard over entire precordium but best heard in fourth interspace on the left. Abdominal examination showed a palpable spleen and liver. There was marked myedema in the upper extremities, and weakness of both grips, more marked in the right hand. The gait was spastic with muscular rigidity.

The neurologic examination showed normal reactions of all cranial nerves. The biceps and triceps reflexes were reduced and knee jerks absent. The Babinski sign on the left was positive, on the right suggestive. Abdominal reflexes were absent and there was no ankle clonus. The finger-to-nose test showed slight ataxia but no intention tremor or dysmetria. Vibratory sense and sense of motion and position were absent in both upper and lower

extremities. Stereognostic sense was lost. There was no disturbance in sensations, either epicritic or protopathic.

Laboratory examinations: Gastric analysis showed no combined acid; total acidity 30. The test for occult blood was negative. Repeated examinations of stools were negative for ova, parasites and flagellates. The blood Wassermann test was negative and urine examinations were negative. The fragility test showed an initial hemolysis of 0.30 and complete hemolysis of 0.45 per cent sodium chlorid. Blood examination on entrance showed a hemoglobin of 28 per cent, the red cells being 1,330,000 per c.mm. and the differential count normal. Blood smears showed anisocytosis, poikilocytosis and abnormal red cells consisting of megaloblasts, some showing nuclear fragmentation and polychromatophilia.

This case is the typical example of the combined syndrome of a well-developed pernicious anemia and a subacute combined cord degeneration.

Case II.—J. F., an American hotel manager, aged fifty-eight years, was admitted to the hospital on February 23, 1925, complaining of pricking sensations of hands and feet. He dates the onset of his illness to about April, 1924, at which time he first noted numbness and pricking sensations in the feet. He had no other accompanying symptoms until July, 1924, when he began to have soreness of his tongue and mouth. At the same time he noted swelling of his left leg which persisted for about ten days. After the swelling of the left leg had disappeared, it became weak. Weakness extended to the right leg soon afterward and walking became very difficult, as he could not coördinate nor accurately control his movements. Recently he has also noted weakness of his hands, so that he was unable to hold objects and frequently dropped them. Since the onset of illness, he has had repeated attacks of sore mouth and tongue and has lost about 30 pounds in weight. There was nothing of especial interest either in the past or family history.

Physical examination showed the patient to be well nourished and well developed with a pasty yellow complexion. Eyes showed a definite exophthalmos with an icteric tint to scleræ—otherwise the eyes were normal. The tongue protruded somewhat to the right with slight atrophy of the mucous membrane particularly at the edges. The lungs were essentially normal. The heart showed slight enlargement to the left with definite arrhythmia and pulse deficit. Both the second aortic and pulmonic sounds were weak. No murmurs were present. The abdomen revealed a palpable liver about 5 cm. below the costal margin. The spleen was not palpable.

Neurologic examination: All cranial nerve reactions were normal. On examination of the reflexes, it was noted that the biceps and triceps jerks were reduced; that the abdominal reflexes were absent and that the knee jerks were increased. Bilateral positive Babinski signs were present and the Romberg was + +. The upper extremities showed continuous movements of the fingers, completely choreoathetoid in character. The finger-to-nose test showed definite dysmetria but no intention tremor. There was definite clumsiness in performing the synergy test. The tips in both hands were extremely weak, more marked on the left than in the right hand. The test for sensations showed loss of vibratory sense and sense of motion and position in both upper and lower extremities. Stereognostic sense was lost. Other sensations were preserved. There was marked hyperesthesia in the tips of the fingers and toes.

Laboratory examinations: Gastric analysis showed a total acidity of 10 and absence of free acid. Occult blood was weakly positive. The urine and blood chemistry examinations were essentially negative. Blood and spinal fluid Wassermann tests were negative. A blood-cell fragility test showed an initial hemolysis of 0.47 and a complete hemolysis of 0.30

per cent sodium chlorid. Blood examination showed a hemoglobin of 80 per cent; red cells, 3,525,000; white cells, 8200; and a normal differential count. Smears showed poikilocytosis and anisocytosis. Platelets were reduced.

This case has besides the subacute combined cord signs also symptoms of involvement of the striated body, a very rare observation. The blood film was not fully developed for the diagnosis of pernicious anemia and was more typical of the preanemic stage.

Case III.—P. C., an American mechanical engineer, aged fifty-seven years, was first admitted on November 2, 1922, complaining of constipation and loss of weight. He dates the onset of his illness to two years before admission at which time he noted marked constipation. He began to lose weight shortly afterward, dropping from about 185 to 152 pounds within a year. In August, 1922, he had the first attack of weakness in his legs, which occurred while dressing. At this time he had unsteadiness associated with vertigo and followed by nausea and vomiting. Ever since the onset of weakness he has had repeated attacks of pricking sensations and numbness in his extremities. His past and family histories were essentially unimportant.

Physical examination revealed a well-developed individual moderately emaciated. His skin was dry and had a yellowish tint and the scleræ had an icteric tint. The tongue was normal. The heart showed a faint systolic murmur, heard best in the fourth interspace on the left side near the sternum. The chest examination was unimportant. The abdomen showed a palpable liver; spleen was not palpable. Neurologic examination at this time was entirely negative.

Laboratory examinations: Gastric analysis showed absence of hydrochloric acid and blood Wassermann test was negative. Urine examinations were essentially negative. Stool examination was negative for blood, ova and parasites. A blood-cell fragility test showed an initial hemolysis of 0.42 and complete hemolysis of 0.32 per cent sodium chlorid. Blood examination on entrance showed: Hemoglobin, 62 per cent; red cells, 1,820,000; white cells, 4600. Differential count was normal. Blood smears showed poikilocytosis and anisocytosis, also showed nucleated red cells consisting largely of megaloblasts, some showing polychromatophilia and nuclear fragmentation.

The blood picture at time of discharge on November 19, 1922, showed: Hemoglobin, 81 per cent; red blood cells, 2,200,000; white cells, 7600.

The patient was readmitted on April 12, 1923, and since discharge he has been improving and gaining in strength. About three weeks before readmission he had several teeth extracted. Since extraction he has again noted weakness of legs accompanied by dizziness. In addition he also developed palpitation and tachycardia.

Physical examination showed a subcyanosis of lips and gums with a decrease in the icterus. The systolic murmur was louder with maximum intensity at the apex and transmitted over the entire precordium both to right and left of sternum.

Blood examination now showed the hemoglobin to be 52 per cent; red cells, 1,590,000; and the white cells 4000.

The patient was transfused three times with whole blood and blood picture at the time of discharge on May 27, 1923, showed a hemoglobin of 78 per cent; red cells, 2,630,000; white cells, 8400.

The patient was readmitted again on March 27, 1924. Since discharge he has felt very good and has been able to work in his office for two and a half months. About two months before his last admission he complained a great deal of dizziness and marked palpitation even on the slightest

exertion. At times he had stiffness of his knees which caused him a great deal of discomfort. For the past six months he developed edema of the ankles and legs.

Physical examination showed at this time a poorly nourished individual with considerable evidence of loss of weight. There was a marked anemic appearance of the conjunctivæ and the mucous membrane of mouth. The tongue had a glossy appearance. Examination of the heart showed a loud blowing systolic murmur at the apex which was transmitted to the right of the sternum. There was marked pulsations of the jugular veins. Reflexes showed knee jerks slightly increased. The Romberg sign was +. There was no disturbance in sense of motion and position. No paresthesias. Vibratory sense was not lost.

On April 13, 1924 he noted some difficulty in walking. Neurologic examination showed loss of sense of position in the toes. Vibratory sense examination gave rise to marked paresthesia. Knee jerks, biceps and triceps were exaggerated.

Blood examination now showed hemoglobin, 40 per cent; red cells, 1,640,000; white cells, 3400.

The patient was transfused again three times with whole blood but the blood picture apparently did not change to any appreciable extent, as at time of discharge on May 17, 1924, it showed a hemoglobin of 46 per cent; red cells, 1,680,000; white blood cells, 4400.

The patient was again admitted on January 20, 1925. Since discharge, weakness and loss of sense of position in the extremities have become more marked. On August, 1924, his legs gave out completely and he was totally confined to bed being unable to walk or use his upper extremities. For past several weeks the flexor muscles of his legs have begun to contract and the knees to bend.

Physical examination now showed an emaciated individual mentally confused. His speech was slow and at times incoherent and hesitating; his memory was very poor. Eye examination showed that the right palpebral fissure and the right pupil were larger than the left. Both pupils, however, reacted to light and distance. The tongue was smooth, glossy and atrophic particularly around the edges of the tongue. The heart did not show any further changes. All extremities showed marked spasticity, more marked in the lower. Flexor muscles of lower extremities showed marked contraction; the thighs being flexed on the abdomen and the legs flexed upon the thighs.

Neurologic examination showed marked increase in knee jerks, biceps and triceps. Bilateral Babinski signs were present. Vibratory sense in both upper and lower extremities was absent. Stereognostic sense was disturbed. There was loss of vesical and sphincter control.

The general course and progress of the patient during stay at hospital was on the decline. No attempt at transfusions or any other form of treatment was made due to his rapid decline. The patient died on April 12, 1925.

This case demonstrates that certain cases of progressive pernicious anemia finally give rise to definite neurologic symptoms which are not demonstrable earlier in the course of the disease.

Case IV.—E. E., an American housewife, aged sixty-three years, was admitted to the hospital complaining of weakness. She dates the onset of her illness to a period several years before admission, at which time she noted a gradual progression of weakness and fatigue even on the slightest exertion. In the last year before admission she also noticed that she felt dizzy and that she fell rather frequently and was unable to control her feet as she used to. Her past and family history was essentially negative.

Physical examination showed a well-nourished individual. The eye and chest examinations were negative. The heart showed a systolic murmur at the apex which was blowing in character and was transmitted to the third interspace. The liver and right kidney were palpable. The spleen was not palpable.

Neurologic examination showed increased knee jerks, and an abortive patellar clonus on the left with no ankle clonus. There was a marked defensive reaction but no definite Babinski on either side. Vibratory sense in the lower extremities was lost. No ataxia or Romberg signs were present.

Laboratory examinations were essentially negative except that the blood examination showed a typical picture of primary pernicious anemia.

Case V.—E. G., an American housewife, aged sixty-seven years, was admitted to the hospital on several occasions for observation, study and treatment. She presented a typical and classical picture of primary pernicious anemia on her second admission January 6, 1925.

On physical examination no evidences of any neurologic changes could be elicited. In September, 1924, she noted for the first time, numbness, prickling sensations and marked paresthesias in the distal phalanges, which have progressively become more marked. The first evidence of definite cord changes was noted on March 10, 1925, when she lost her vibratory sense in the lower extremities. No further neurologic change has developed since then.

Conclusion. In our observations, we find that at least 80 per cent of our cases of pernicious anemia presented some form of neurologic manifestation.

It appears that the loss of vibratory sense is almost invariably the earliest sign of neural changes in pernicious anemia and not infrequently a diagnosis of the disease and subsequent development of cord changes were predicted in spite of a normal blood picture.

Cord changes may precede the characteristic blood picture of pernicious anemia, and in such cases the progress of the disease is more rapid, remissions are less frequent and prognosis more serious. Neurologic manifestations are apparently limited to the cord, particularly involving and causing marked tract degeneration of the spinocerebellar and posterior column tracts.

Cerebral involvement are not infrequent, but manifestations are more diversified in type and cannot be localized with the same degree of accuracy as in the spinal cord.

Finally we wish to emphasize that cord findings in pernicious anemia are more commonly present than have been reported, and that the general practitioner should safeguard his observation and interpretation of the neurologic findings, as very often a diagnosis of neuritis, tabes and of other erroneous diseases is made in the early stages of the disease.

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PRESSURE CHANGES IN THE BILIARY TRACT.*

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In the past most of the experimental work on the physiology of of the extrahepatic biliary ducts has been done on anesthetized animals through acute experiments. The anesthetic and various other factors have influenced the results. In order to overcome these objections, and to determine the bile pressures in the intact animal, a method was developed to observe the gall bladder and common duct pressures synchronously by means of a cholecystostomy tube and a T tube in the common duct of the dog. In this work the operative procedures were carried out under anesthesia. The cholecystostomy tube was placed in the gall bladder and the T tube in the common duct near the duodenum. These tubes were allowed to heal in position before observations were made on the intact animal. Thus these pressure readings were not complicated by any external influences or discomfort of the animal. This is an ideal way of studying the pressures in the common duct and gall bladder, as well as the mechanism of the cystic duct and the pressure relationships on either side of it. Besides recording the biliary pressures in several dogs prepared in this manner, a few acute physiologic experiments on the cystic duct of the dog were made, and certain other constant phenomena observed and studied.

* This work was submitted by Dr. Potter to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery, June, 1925.

During the experiments certain pertinent questions with regard to biliary pressure arose which were variously investigated as follows:

1. The determination of the average biliary pressure in the intact dog.
2. The effect of diet on the average biliary pressure.
3. The study of rhythmic pressure waves in the common duct.
4. The confirmation of rhythmic pressure waves in the gall bladder.
5. The relationship of the pressure curve of the common duct to that of the gall bladder.
6. The effect of cholecystectomy on the pressure curves in the common duct.
7. The effect of infection on the pressure curves in the gall bladder and common duct.
8. The study of the sphincter and the pressure relationships at the neck of the gall bladder.
9. The emptying of the gall bladder as studied under the fluoroscope with the use of opaque mediums.

Review of the Literature. The pressure which the sphincter of the common bile duct will maintain has been determined by several observers by means of a manometer attached to a cannula. This was usually placed in the sectioned common duct pointing toward the duodenum, through which when open the pressure at which the sphincter gave way was observed. The results were influenced by the anesthetization of the animals, and possibly also by impairment of the nervous control in the sectioning process (tabulation).

The effect of external stimuli and diet on the biliary pressure maintained by the sphincter has been determined by few observers. Archibald noted that touching the duodenal mucous membrane with hydrochloric acid or pinching it raised the sphincter tone for a few seconds. McWhorter found that magnesium sulphate in the duodenum lowered the sphincter tone from 50 to 100 mm. of water. Jacobson and Gydesen observed the same phenomenon, and also that acids and peptone lowered the sphincter tone. Cole has some evidence that the isolated gastric contents influence the pressure which the common duct sphincter will hold. If one assumes that the biliary flow controls the pressure to a certain extent the following observations have a bearing on the problem.

Martin and Copeman noticed that in the biliary fistula of man there was an increased flow of bile after meals. Auster and Crohn report that bile flows into the duodenum even in the fasting state, while the amount is increased after the ingestion of hydrochloric acid, peptone, bile and fats. Jacobson and Gydesen found an increased flow after certain foods. Rost observed an increased flow after acids. Okada, who experimented with many drugs and foods, noted that starvation decreased the biliary flow, while water, sugar, starch and soda had no effect. The flow was increased by

bread, butter, meat, eggs, acids, peptone, extracts and bile. Rost and Klee and Klüpfel found that in the fasting state bile was discharged into the duodenum at long intervals, whereas peptone and food caused rapid spurts.

Although there are no records of rhythmic pressure waves in the common duct, there are some observations on the subject. Doyon[12] noted contractions of a peristaltic type in the common duct; Westphal observed four contractions a minute of the lower end of the common duct in rabbits and cats, and Copeman, in a case of biliary fistula, noticed that "The act of secretion was found not to consist of a continuous oozing, but short periods of rest followed by a flow in a series of jerks, caused by peristaltic contraction." Harley thought that the "jerks" were mechanical, due to the emptying of the tube. Gerald observed rhythmic contractions in isolated strips of common duct from sheep which responded to certain drugs with a characteristic action. Rost and Klee and Klüpfel record the fact that bile is discharged into the duodenum in spurts. Klee and Klüpfel state that one occurs as each peristaltic wave passes the pylorus.

Rhythmic waves of changing pressure have been observed in the gall bladder during many investigations. Doyon[12] was the first to record them. Okada,[39] using a distended balloon in the gall bladder of the anesthetized dog, found that the rhythmic waves were increased in number when oil, food or hydrochloric acid was injected into the duodenum. Bainbridge and Dale, and Macht have also reported rhythmic pressure waves in the gall bladder. Mann and Giordano noticed waves in animals with fistulæ of the common duct, which could be attributed to the movements of the gall bladder. They found also that in the dog the rhythmic movements ceased when the pressure was more than 340 mm. of water. Freese, by stimulating the proper nerves, determined the contraction pressure of the gall bladder to be about 214 to 313 mm. of Ringer's solution.

With regard to the emptying of the gall bladder, Doyon,[13] in 1894, said that stimulation of the central end of the vagus caused the sphincter of Oddi to relax and the gall bladder to contract. Meltzer,[35] reasoning from his law of reciprocal innervation, thought that this relationship should exist, but there are no records to substantiate it. Furthermore, observers agree that the gall bladder does not contract in the same manner as the urinary bladder.

Eisendrath and Dunlavy, Judd and Mann, Oddi,[36] Rost and many others have observed that following cholecystectomy the stump of the gall bladder and the biliary ducts dilate. Walzel notes that when a rather large stump of the gall bladder is left it dilates to form another gall bladder. Sweet finds that the partial saccules are also dilated. Judd and Mann have observed that if the sphincter of Oddi is cut the ducts do not dilate after cholecys-

tectomy, and if it is not cut at the time of operation the tonicity of the sphincter is lost sometime afterward. In this connection Rost notes that after this operation certain dogs are continent as regards the sphincter of Oddi, while others dribble bile, and peptone does not cause spurts of bile from the papilla of Vater, as in the normal animal. Klee and Klüpfel have confirmed his findings. Rost believes that the determining factor is the length and strength of the sphincter of Oddi. Billard and Cavalié have noted that the flow of bile increases after ligation of the cystic duct. Mann,[27] in 1924, collected all of the experimental and clinical data concerning dilatation of the extrahepatic biliary tract and the tone of the sphincter of Oddi following cholecystectomy.

In studying the pressure relationships in the cystic duct, that is, the pressure necessary to cause a flow through the duct with no pressure in the part studied, Mann found that the cystic duct never maintained a pressure of more than 30 mm.

In trying to study the emptying of the gall bladder under the Roentgen ray Winkelstein ingeniously sewed four silver discs on the serous surface of the gall bladder of the dog. He was unable to discover any change of size before or after feeding. Abramson injected the gall bladder of the dog with neosilvol, but was unable to see it empty under the fluoroscope. Nevertheless, in a dog with a cholecystostomy tube, which was injected with a 150 per cent solution of sodium iodid, he saw opaque material spurt from the gall bladder once during a long period of observations.

Matsuo reports the emptying of the gall bladder following duodenal lavage with magnesium sulphate in accordance with the method of Lyon. Graham's recent test for disease of the gall bladder has shown the slow filling and emptying of the gall bladder by opaque dyes secreted by the liver. It has not shown any marked contraction, although some evidence has been obtained that it does empty. Silverman and Menville observed a decrease in the size of the visualized gall bladder following the duodenal instillation of magnesium sulphate.

One of the most interesting observations on the emptying of the gall bladder was made by Boyden. In a study of the gall bladder in a large series of cats killed after ingesting various foods he noted that the gall bladder was empty after a meal of fat. Whitaker, using sodium tetraiodophenolphthalein as an opaque medium, was able to obtain a beautiful picture of the gall bladder and to show a marked decrease in the size of the shadow after feeding an animal a meal of fat.

Winkelstein and Aschner inserted a cannula into the common bile duct, from which a portion of the hepatic bile had been diverted, and after lavage of the duodenum with magnesium sulphate, obtained dark-colored bile.

Bainbridge and Dale noted that the neck of the gall bladder reacted to epinephrin differently from the rest of the gall bladder.

Methods Used in Experimental Work. *Operative Technique.* In the study of the pressures and the rhythmic pressure waves in the common duct and gall bladder, gentle, quiet dogs were selected and trained to lie perfectly quiet on the left side for long periods. The training period lasted a week or more. At the end of this period the upper abdomen was opened in the median line under ether anesthesia, with the usual sterile precautions. The common duct was isolated and a short longitudinal slit made near the duodenal

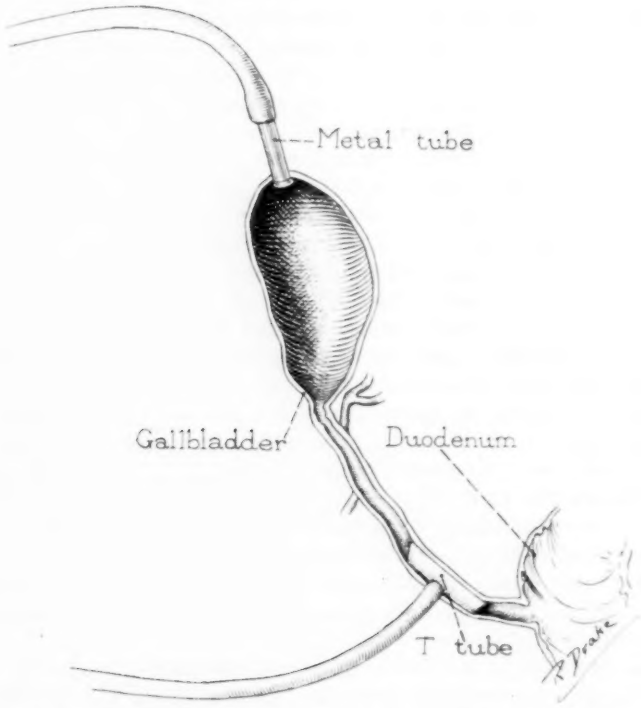

FIG. 1.—Devices by which observations were made in experiments.

end, into which the short ends of a rubber T tube about 4 mm. in diameter were carefully slipped, and the walls approximated with very fine silk sutures to prevent leakage. Care was also taken to avoid injuring the nerves around the duct.

In the dome of the gall bladder a small opening was made, into which was placed a short metal tube with a flange, or a small rubber T tube. These were held in place by means of a purse-string suture. The rubber T tube seemed to be the most satisfactory. Through separate stab wounds in the right rectus muscle the ends

of the tubes were brought to the outside and the incision in the median line closed in the usual manner with catgut and linen (Fig. 1).

In the early experiments the animals were prevented from pulling out the tubes before they became accustomed to them by means of a collar, but as this collar was not wholly effective a different method was devised. The external ends of the tubes after being brought out through the lateral abdominal wall were tucked back under the skin superficially. When the animal became aware of their presence they were brought to the exterior through the original stab wound. When not being used for observations the distal ends of the rubber tubes were tied shut by linen thread so that the usual biliary flow continued down the common duct through the short end of the T tube into the duodenum. Animals prepared in this way ran about normally, with the two tubes healed in position.

Methods of Routine Observation. After a few days, when the abdominal wound had healed and the dogs were again accustomed to lying quietly, the pressure readings were taken by having the animal lie on its left side on a comfortably padded table. The room was kept quiet and the animal allowed to sleep. A little strenuous exercise before the experiment often induced the dog to doze during the observations. When the animal was peacefully settled cannulæ were inserted into the opened ends of the exposed tubes in the lateral abdominal wall. From the cannulæ rubber tubes led to upright glass tubing of 2 mm. inside diameter. These rods were attached to a meter scale whose zero reading was placed at the animal's medium abdominal raphe. The pressure was then recorded in millimeters of the bile which flowed out through the cannulæ into the upright glass tubing attached to the scale. In this paper the bile pressure is considered equivalent to water pressure. When not in use the cannulæ and tubes were kept in an alcoholic solution to prevent infection.

In the first experiments readings of the pressures were taken every ten minutes. The time interval was gradually decreased until the gall bladder and duct pressures were read every half minute. A few records were made of the duct pressure every ten seconds. As it seemed best to take a continuous record an apparatus[40] was developed, the principle of which was to follow the meniscus of the bile by means of a hand-controlled writing point, which recorded the fluid level on a moving drum. These records showed slight variations and could be measured and studied later.

In studying the effect of diet on the pressure the animal after fasting for eighteen hours was fed the test meal. The records were taken from forty-five minutes to one and a half hours later.

In a small series of acute experiments the pressure relations at the neck of the gall bladder in the dog were studied with the animal in the dorsal position. In these the abdomen was opened in the

median line and the viscera packed off with warm gauze and towels. A purse-string suture held a cholecystostomy tube in the gall bladder, while a cannula was placed in the hepatic end of the sectioned common duct. Each tube led to a manometer and the pressure was varied on one side or the other of the neck of the gall bladder and the cystic duct, following which the pressure on the opposite side was noted. At the close of the experiment the dogs were made to rebreathe in an attempt to produce contraction of the gall bladder.

Roentgen ray examinations were made on a dog with a cholecystostomy tube. Through this a barium solution was injected and the animal placed under the fluoroscope first on one side, then on the other.

Results of Experiments. *The Average Biliary Pressure in the Intact Dog.* As the average biliary pressure is varied by diet, and the gall bladder pressure may be greater than the duct pressure, it was thought best to average all the satisfactory duct and gall bladder readings for normal dogs to get the average pressure in the biliary system of the normal intact dog. This was found to be 120 mm. of water. A more important figure is the norm obtained by grouping the records in divisions of 75 mm. of water pressure.

TABLE I.—PRESSURE IN BILIARY SYSTEM OF NORMAL DOG.

Millimeters of water pressure	0–75	75–150	150–225
Number of readings	3	29	5

These figures show that the majority of the readings lie between 75 and 150 mm. of water pressure. This norm, as stated, includes both duct and gall bladder readings, and probably represents quite accurately the actual pressure in the biliary system of the quiet, intact dog.

The average pressure in the gall bladder is greater than that in the duct. In the gall bladder it was 141 mm., whereas in the duct it was 117 mm.

The Effect of Diet on the Average Biliary Pressure. The three procedures used in testing the effect of food on the biliary pressure were fasting, milk diet and dog biscuit diet. Milk caused a constant marked elevation of pressure, fasting gave the lowest pressure, while dog biscuit held a middle position.

TABLE II.—EFFECT OF DIET ON AVERAGE BILIARY PRESSURE.

	Fasting.	Dog biscuit. Pressure in mm.	Milk.
All combined duct and gall bladder readings	93.4	110.8	126.9
In a single dog	95.0	120.0	153.0
Duct	95.0	109.0	130.0
Gall bladder	114.0	129.0	182.0

When the duct and gall bladder pressures are separated the same relationship to diet is found, as would be expected. Furthermore, it is again apparent that the pressure in the gall bladder is greater than that in the common bile duct.

If the experiment is continued long enough after a milk or ordinary diet the pressure gradually drops. The rise of pressure after a milk diet, above the fasting reading, is easily demonstrated by taking a record of the pressure in the fasting dog, feeding the animal milk while on the table and allowing it to sleep an hour. After the nap the record will show a marked elevation of pressure.

The Rhythmic Waves of Pressure in the Common Duct. The common duct curves show three constant rhythmic variations in pressure which probably have a physiologic import. The usual record shows a primary type of wave, which is large and rhythmic, with a gradually ascending up slope and a rather abrupt down slope. The second type of wave is superimposed on the foregoing, is of medium size and occurs about five to seventeen times a minute. Finally there is the third wave which is small, and synchronous with the respiratory movement.

The following records show these rhythmic waves in as many dogs. One is taken with the respiratory recorder to show the relationship of the pressure waves to the respiratory curve. There is also a second marker to show the number of the medium-sized waves each minute (Figs. 2 and 3).

FIG. 2.—Rhythmic pressure curves of common duct.

When the duct pressure is first registered it often shows a distinct "peak" in the early part of the curve as it rises from zero (Fig. 4). In this connection it may be noted that when the intraductal pressure is raised from without it does not drop smoothly and regularly, but in a series of jumps. These may be synchronous with respiration, but we have not definitely determined this point.

The Rhythmic Waves of Pressure in the Gall Bladder. The rhythmic waves of pressure change in the gall bladder have been confirmed, but no observations as to the effect of diet and other stimuli were made. The respiratory waves in the gall bladder were much greater than those in the common duct, due probably to the greater volume of fluid and surface to be pressed on.

The Pressure Relationships in the Gall Bladder and Common Duct Curves. There are two important findings when the common duct and gall bladder curves are studied together: (1) The pressure in the gall bladder may be higher than that in the common bile duct; (2) there is what might be called a "reciprocal pressure change,"

that is, the pressure in the gall bladder rises as that in the duct drops, after which the curves approach each other and meet, to separate again and repeat this relationship (Figs. 4 and 5).

A third constant finding in synchronous records of the gall bladder and common duct pressures is the fact that the pressure in the gall bladder rises more slowly than that in the duct, due probably to the slow filling and distention of the bag.

The "peak" of pressure at the early part of the curve and the gradual fall of pressure after a meal have been described (Fig. 4).

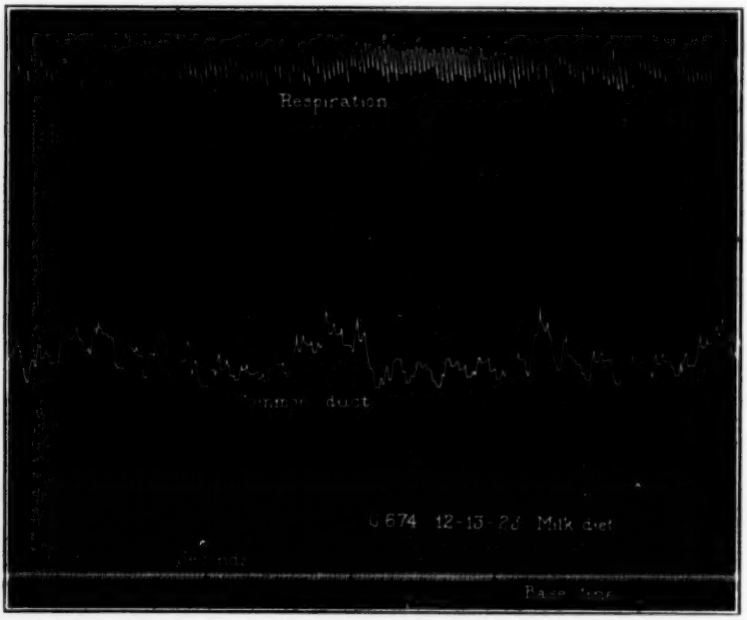

FIG. 3.—Pressure curve of common duct taken with respiratory recorder and second marker at base.

Besides the reciprocal pressure relationship, the slower rising of the gall bladder curve, and the fact that the pressure in the gall bladder may be greater than that in the duct, the curve in Fig. 4 illustrates another phenomenon, probably mechanical, which may be seen after a milk diet when the gall bladder and common duct pressures are recorded together. At the height of the curve the two pressures may separate widely to come together later as the pressure drops. The separation of the curves is probably caused by back pressure from the T tube, due to the fact that at the maximal flow the lumen of the short end of the T tube is not great enough to take the bile away, but backs it up into the gall bladder, raising the pressure. This would seem probable, as the two curves approach each other when the flow and pressure gradually drop

after the milk diet. Furthermore, it is not seen in the curve after the ordinary diet.

Three of the dogs showed the reciprocal pressure relationship in varying degrees. The fact that the gall bladder pressure is at times greater than the duct pressure is a general finding. In the reciprocal relationship the fact that from a common point the duct pressure drops while the gall bladder pressure rises, gives the impression that the phenomenon is physiologic, not mechanical.

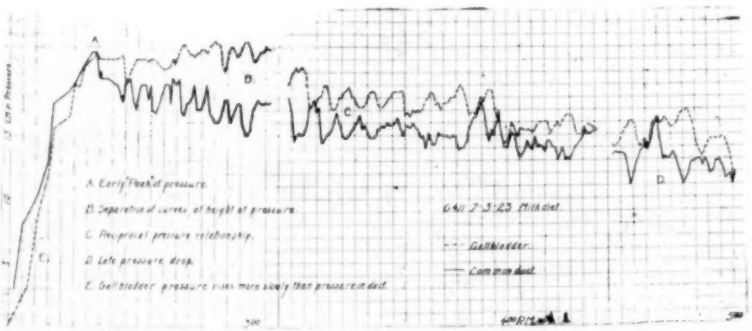
A. Early Peaked pressure.
B. Separation of curves, of height of pressure.
C. Reciprocal pressure relationship.
D. Late pressure drop.
E. Gall bladder pressure rises more slowly than pressure in duct.
Gall bladder.
Common duct.

FIG. 4

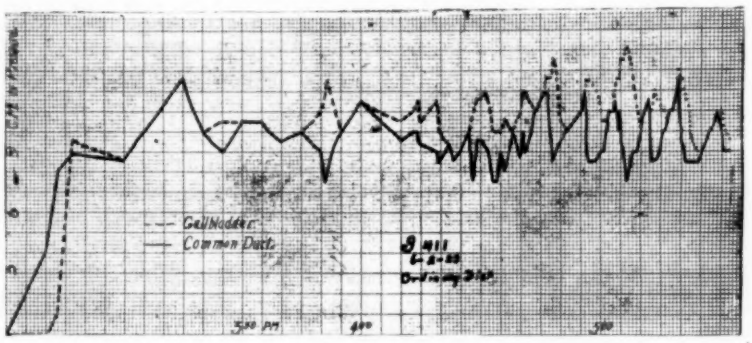

FIG. 5

FIGS. 4 and 5.—Synchronous records of pressures in gall bladder and common duct, illustrating reciprocal pressure change.

The Effect of Cholecystectomy on the Pressure Curves in the Common Duct. A limited number of records were made following cholecystectomy. These show a marked increase in the common duct pressure (235 mm.) and an increase in the amplitude of the large rhythmic waves (Fig. 6).

The Effect of Cholecystitis on the Pressure Curves. The effect of cholecystitis on the waves of pressure in the gall bladder and common duct is to flatten them out, causing a straight line on the

record, and the duct and gall bladder curves run parallel (Fig. 7). The high peaks in Fig. 7 are due to deep sighing respirations.

FIG. 6.—Record showing pressure curves of the common duct sixteen days after cholecystectomy.

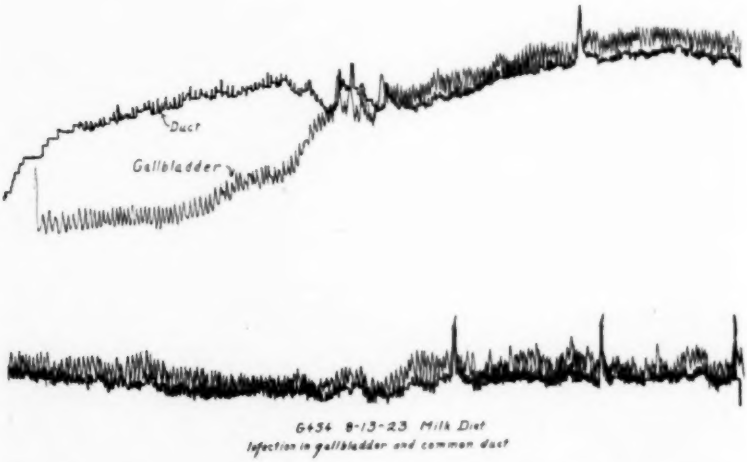

FIG. 7.—Record showing the flattening and the parallelizing of the curves when the gall bladder and common duct are infected.

The Sphincter and the Pressure Relationships at the Neck of the Gall Bladder. The pressure relationships at the neck of the gall bladder were studied in the intact dog and in acute experiments. In the anesthetized animal a low pressure, about 30 to 80 mm. of water, was held from both sides. The pressure which the gall bladder neck and cystic duct could hold was decreased by raising the pressure several times to a high point on either side. After a short rest the pressure maintained would return to the original reading. Apparently the high pressure ironed out the mechanism for a short time.

The rebreathing of the dogs did not cause contraction of the gall bladder.

One intact animal in excellent condition was able to hold 150 mm. of water pressure from both sides by means of the resistance mechanism at the neck of the gall bladder.

The Emptying of the Gall Bladder as Studied under the Fluoroscope by the Use of Opaque Mediums. One dog was examined under the fluoroscope. Through a cholecystostomy tube the gall bladder was filled with a small amount of barium solution and the animal studied, lying first on one side, then on the other. The gall bladder appeared to undergo a movement which may have been peristaltic or "squashing," due to rhythmic constriction. From the neck of the gall bladder spurts of opaque material were projected at intervals, apparently rhythmically.

Discussion. The average sphincter pressure as found in the normal intact animal closely parallels the pressure readings of the more recent observations during acute experiments, and is much lower than the readings of earlier investigators.

If the bile pressure is determined by the bile flow to any extent the effect of various diets could be anticipated somewhat.[2, 3, 8, 10, 19, 21, 22, 35, 38] Fasting might be expected to produce the lowest pressure, whereas milk and the mixed diet found in dog biscuit would cause a greater pressure. Furthermore, the fact that bile is needed in the assimilation of the fats in the milk would make it seem reassonable that the pressure would be greater with a milk diet than with a diet of dog biscuit, although according to Boyden's work a pure fat diet might cause the reverse.

The large waves in the common duct are, we think, unquestionably due to the mechanism of Oddi's sphincter on the flow of bile. This idea is supported by the slow rise and rapid drop of the wave, which would be expected from a gradually increasing pressure relieved by the opening of the sphincter of Oddi. Rost, and Klee and Klüpfel have shown that bile is discharged at intervals in spurts into the duodenum. In addition, the increase in the amplitude of the waves following cholecystectomy gives the impression that they are an intraductal rather than an extraductal event. Pressure from the adjacent duodenum must also be borne in mind as a possible source of the large waves. The medium waves may be due to: Contraction in, and pressure from, adjacent organs, peristalsis in the duct itself, or to some contraction in the gall bladder. This last is apparently ruled out by their presence when the gall bladder is not functioning for any reason, and after cholecystectomy. The most likely adjacent organ to cause a disturbance in the pressure reading of the duct is the duodenum. It was not possible to determine any relationship to any pressure waves in the common bile duct to those in the duodenum, that is, peristalsis of the duodenum. Furthermore, the waves in the duodenum, do not bear any resemblance to the curves of the common duct which have been shown. The effect of respiration on the pressure curves can practically be ruled out with the exception of sneezing, coughing and straining movements, which cause marked changes in abdominal pressure. The ordinary respiratory effect on the pressure

is a small superimposed wave which is greater in the gall bladder curve than in the common duct, due probably to the greater surface and volume of the gall bladder. The fluctuations due to breathing can easily be checked and shown to be synchronous with a respiratory record. The peak in the curve at the start of the record is apparently due to a resting of the sphincter mechanism by the sudden release of pressure when the bile flows into the tubing. As the pressure mounts it goes for a moment above the average pressure before the sphincter mechanism is "touched off" into its usual action. The dropping of the duct pressure by jumps would also seem to indicate that the intraductal pressure had a share in controlling the sphincter, that is, the high pressure causes the sphincter to open allowing the pressure to drop. Following this the sphincter closes, checking the drop, but, the pressure still being too high, the sphincter again opens. This phenomenon of dropping by jumps may have some relationship to respiration, but this point has not been determined. The fall in pressure after a meal certainly suggests that the bile flow affects the pressure.

It is barely possible that there are two types of pressure waves in the gall bladder: One caused by a squashing action and another by a contraction of a peristaltic nature. The fluoroscopic examination cautions us to leave this question open, however.

The most significant observation brought out in this work is the "reciprocal pressure" relationship in the curves of the gall bladder and common duct. While more records are necessary, there is no question but that the ones shown are suggestive. If the drop of pressure in the duct is interpreted as the opening of Oddi's sphincter, and the rise of pressure in the gall bladder as the contraction of its musculature, Meltzer's law of reciprocal innervation is exhibited as applied to the sphincter of Oddi and the musculature of the gall bladder. However, it is apparent that the gall bladder does not contract completely.

The flattening of the curves in cholecystitis with the tract acting as a conduit may be of practical importance. Bollman, Mann and Depage have shown that there is little concentration in the inflamed gall bladder. These two observations would tend to show that dyes excreted by the liver as opaque mediums for Roentgen ray examinations, or as bactericidal agents in inflammatory conditions of the biliary tract do not move slowly enough or become sufficiently concentrated to be effective at these times. The breaking down of the contraction mechanism in itself may be an important factor in preventing concentration.

The rise in the duct pressure and the amplitude of the sphincteric waves following cholecystectomy might be anticipated from the observations of others on the extrahepatic dilatation of the biliary ducts following cholecystectomy. This certainly suggests a "pressure" dome effect. The latter may be one of the mechanisms for

furthering the absorption of substances from, and concentration of, bile in the gall bladder.

The fact that the neck of the gall bladder is capable of maintaining pressure from either side is another interesting observation, previously recorded by Mann, whose pressures were not quite so high. The exact physiologic relationship and importance of this fact have not been determined.

The fluoroscopic observations of the emptying of the gall bladder in rhythmic spurts are not conclusive. However, with the foregoing data it is very suggestive that there is a sphincterlike mechanism at the neck of the gall bladder. The spurts may have been due to barium particles sticking in the cystic duct. In further work a solution of sodium iodid should be used to overcome this objection.

In view of the curves previously shown, it would seem that during the contraction of the sphincter of Oddi the bile is forced into the gall bladder. That most, if not all, bile enters the gall bladder is shown by the appearance of excreted dye almost simultaneously in the duct and gall bladder. Here it is concentrated, and when Oddi's sphincter relaxes a variable amount of gall bladder contents is forced out, perhaps none at times, but with the next closing more bile is forced into the gall bladder. At the same time that the bile is being concentrated it may be that substances useful to the organism are being extracted from the bile. The "pressure dome" effect of the gall bladder is probably a mechanism helpful in concentration. During the fasting period, with long intervals between relaxations, there is ample opportunity for considerable concentration. It is possible that the sphincteric control at the neck of the gall bladder may play a part during these fasting periods. With the ingestion of food and the outflow of bile this more concentrated bile by a gradual pumping action is slowly washed out, to work more perfectly in assimilation. That all is not washed out is seen by the retention of dye sometimes for nearly a week. This outflow may be a most important item in controlling the secretion of bile, as pointed out by Mann.[29]

Summary. The average sphincter pressure in the intact dog is 120 mm. of water. The pressure varies according to the diet. Of the diets studied, fasting gives the lowest pressure and milk the highest.

In the pressure curves for the common duct, besides the small respiratory waves, there are large waves, probably of sphincteric (Oddi) origin, and medium waves, possibly due to peristalsis in the musculature of the common duct. The rhythmic waves of pressure change in the gall bladder have been confirmed.

The pressure in the gall bladder is greater at certain periods than that in the common duct. There also appears to be a reciprocal pressure relationship in the gall bladder and common duct.

Infections in the biliary apparatus cause a flattening of all curves

and a destruction of the contraction mechanism, as shown by pressure variations. Cholecystectomy caused an increase in the common duct pressure and in one case an increase in the amplitude of the sphincteric waves.

There is a sphincter-like mechanism at the neck of the gall bladder capable of maintaining a slight pressure from both sides.

In one instance fluoroscopic examination showed barium being discharged in rhythmic spurts from the gall bladder.

TABLE III.—PRESSURES MAINTAINED BY THE SPHINCTER OF THE COMMON BILE DUCT.

Observers.	Animals.	Pressure, mm.
Oddi[37]	Dog	625
Archibald	Dog	180–330
Judd and Mann	Dog	100–150*
Mann[26]	Dog, cat, goat, rabbit, guinea pig	75–100
	Rat, gopher	30
Jacobson and Gydesen	Dog	150
McWhorter	Dog	100–200
Cole	Dog	150
Winkelstein and Aschner	Dog	60–65

* This was reduced to less than 40 mm. by excision of the gallbladder.

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SUBSTERNAL THYROID.*

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Substernal thyroid has been variously designated as intrathoracic, retrosternal, mediastinal goiter or struma profunda. This condition was first described as an anatomic finding by Haller[1] in 1749. From the clinical aspect substernal thyroid has apparently been neglected, as witnessed by the paucity of reports in the literature, although as early as 1830 Lingl[2] described the clinical picture. However, anatomists and surgeons have, from time to time, drawn attention to the occurrence of goiters within the chest. From our personal experience and that gleaned from an analysis of the literature, it is not as rare as it is usually thought to be. This apparent rarity may be explained by the fact that the presence of such condition may readily be overlooked; for a substernal thyroid may be symptomless and when producing recognizable features, is frequently mistaken for other conditions that may occur within the thorax.

Because of these facts and because of the inoperability of many cases, this condition has been chiefly of interest from the pathological, anatomical and occasionally from the surgical standpoints. It is therefore the purpose of this paper to draw attention especially to the symptoms and physical findings of this type of mediastinal tumor.

Clinically, substernal thyroids are of two kinds, either a retrosternally placed parent thyroid or an intrathoracically placed aberrant thyroid. Aberrant thyroids are classified as false aberrant thyroids, or glandular masses that are attached to the main thyroid either by fibrous or other tissues, and true aberrant thyroids, or glandular masses that have no connection with any other thyroid tissue that may be present.[3,4] The latter are the results of congenital *anlagen*.

The terms substernal, intrathoracic, aberrant and retrosternal thyroids are very loosely employed in the literature, especially by surgeons, who are prone to call a lobe that has slipped slightly behind the manubrium a retrosternal thyroid. The terms false and true aberrant thyroids are also very misleading. A mass of thyroid is either aberrant or not. It would therefore clarify the subject to limit the terms as follows:

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1. Substernal, to abnormal descent of the main gland, a lobe or an adenoma.

2. Intrathoracic goiter, to aberrant glands growing within the chest.

A brief consideration of the etiologic factors concerned in the production of these tumors is apropos. Thyroptosis or the descent of a normally placed thyroid is responsible for the misplacement of an entire gland, or either lobe of the gland. Especially is this true of the hyperplastic and enlarged types of glands. The dragging influence, the consequence of respiratory efforts, the dragging effects of a tumor growing within the substance of a normally situated thyroid, the effects of tight collars, and training by manipulation for cosmetic purposes, and even gravity itself, are all pathogenic influences in the causation of retrosternal goiters. Because of these latter mentioned factors this condition is therefore more frequently seen in older than in younger individuals.

Aberrant thyroids have been found in various situations from the base of the tongue to the pericardium and lungs. It is for this reason that experimental myxedema is difficult to produce in animals, especially in dogs. Schwartz and Thompson[5] found in 30 dogs, successively examined, that in 24 there had been thyroid rests about the arch of the aorta. His at one time believed that the lateral lobes of the thyroid gland developed in the fourth branchial cleft. Should this be the case, although still a matter of dispute amongst embryologists, it would give an embryologic basis for the occurrence of such accessory or aberrant thyroids discussed in this paper; namely, the substernal variety. On the other hand, the thymus gland develops from the third branchial cleft and descends to a position behind the sternum. It is therefore conceivable that in its descent into the thorax, it may drag part or the entire thyroid into the mediastinum. Furthermore, the close proximity of the points of origin of the thyroid to the arch and ascending portion of the aorta in fetal life, and the subsequent migration of the heart into the chest, may drag thyroid rests into the chest. These *anlagen* may subsequently take on either a hyperplastic or other pathologic changes similar to those induced in the normally situated thyroid gland. Various influences, such as endemic conditions, menstruation, puberty, menopause and pregnancy may affect the aberrant gland in the same manner as the normally situated gland.

Substernal thyroid may be fixed or mobile. Violent respiratory efforts may force a goiter already within the chest into the neck or *vice versa*, thus giving rise to a condition known as "spring goiter," "goiter mobile," or "wandering goiter." On the other hand, it is more usual, owing to its size or to adhesions, that the goiter remains fixed within the chest, so that escape through the upper outlet of the thoracic cavity is impossible.

The size of aberrant glands may vary from that of a tiny nodule to a structure several times larger than the normal thyroid itself, the size and shape of the mass depending on the yielding property of the surrounding tissues during the development of the gland and to the rapidity of growth. These rudimentary glands, as has been stated, have been found anywhere from the base of the tongue to the root of the aorta, within the pericardium and the pleura. In the latter it may reach such size as to cause severe symptoms of lung compression and even prevent the normal lung expansion.

These glands may supplement or take the function of the normal gland itself. Therefore, they are subject to the same pathologic changes in about the same proportion as is common to the normally situated thyroid, viz; a parenchymatous enlargement with colloid involution being most frequent. An unusual, though interesting, form is the development of large cysts due to the breaking down of an adenoma.[6,7] Malignant changes are also common.

Incidence. From 1912 to 1920, Czermack studied all the goiter material occurring in the Innsbrucker Clinic, and out of 1473 goiters present, 487, or 32 per cent, were retrosternally situated. Of these 487 retrosternally placed goiters, the right lobe was retrosternal in 251 cases, or 51 per cent. The left lobe in 148 instances, or 31 per cent, and the isthmus 29 times, or 6 per cent. The left and right lobes together, he found 59 times, or 12 per cent. Reimach found 31 substernal out of 162 cases of goiter. Class found 10 out of 106; Kocher found it in 10 per cent of his cases. Monnier[8] out of 670 cases of goiter found 117 to be substernal, 17 deeply intrathoracic From January 1, 1917, to June 6, 1920, 4006 thyroidectomies were performed in the Mayo Clinic[9] for simple colloid and adenomatous goiters. Of these 542, or 13.5 per cent, were found to be partially substernal, and 25 per cent of these classified as intrathoracic.

In a series of 495 teleoroentgenograms taken in conjunction with the routine cardiovascular examination, we found 6 cases of substernal thyroid. There is no doubt that where a greater and more varied series of Roentgen ray examinations of the chest is made, the incidence is greater than that which has been reported in the literature. It seems from our experience that the roentgenologists are unaware of this fact, for they invariably diagnose such cases of substernal thyroid as aneurysm of the aorta.

In our review of the literature, we have found that about 80 per cent of retrosternal thyroids occur in women; and that the age is most common between fifteen and thirty-five years. One can readily conceive from the above the frequency of struma profunda; for about 7 to 10 per cent of all cases of goiter fall into this category.

Diagnosis. The diagnosis of this condition is only possible by an accurate analysis of all the symptoms presented. These may

be grouped under two distinct headings: (*a*) Remote or toxic symptoms induced by hyperactivity of the gland or hyperthyroidism. (*b*) Pressure symptoms resulting from mediastinal involvement and its adjacent structures.

The toxic effects of this anomaly may vary from that of a mild thyroid hyperactivity to that of marked hyperthyroidism, with symptoms of a fully established Graves disease, yet without visible thyroid enlargement of the neck. Frequently, obscure cases, presenting only an auricular fibrillation of unknown origin in a heart, apparently not diseased, is due to a small goiter that has had a tendency to extend down behind the sternoclavicular joint or to an aberrant intrathoracic thyroid. All such cases of auricular fibrillation, the type often designated as idiopathic, in the absence of the usual etiologic factors, should be carefully investigated as to the absence or presence of a substernal thyroid. Any patient who presents himself or herself with symptoms suggesting an overactivity of the thyroid, (rapid pulse, nervousness, irritability, debility, and so forth), plus any sign or signs of intrathoracic pressure, should receive the benefit of fluoroscopic and Roentgen ray investigations to determine the presence of an intrathoracic goiter.

The symptoms caused by compression of the various structures within the thorax are too well known to necessitate recapitulation. However, of special interest are those cases simulating asthma, chronic emphysema, aneurysm of the aorta, mediastinal and intrathoracic malignancy, etc.

The fixation of the trachea by an intrathoracic goiter may inhibit the normal excursion of the larynx; an important diagnostic factor. By placing the finger deeply in the suprasternal notch, one feels a mass which has the consistency characteristic of a goiter: firm elastic and finely lobulated, and at the same time rising with the larynx during coughing and swallowing. In contradistinction to an aneurysm there is no palpable pulsation of an expansile character. Oliver's sign (tracheal tug) is never present in substernal thyroid. Wuhrmann[10] claimed that a high degree of tracheal stenosis, a deeply placed larynx and the absence of palpable thyroid in the normal situation, should suffice to render a diagnosis of retrosternal struma.

Certain muscular movements, such as sudden exertion or flexion of the head, may cause the mass to become wedged in the upper thoracic inlet. This results in spells of obstructive breathing, coughing and a choking sensation. Such intermittency is not produced by any of the other varieties of mediastinal growths, except esophageal diverticula. When the latter is present, the shadow found on Roentgen ray examination is not constant. This can be clearly differentiated from substernal thyroid by careful barium studies. Signs and symptoms of mediastinal compression associated with a visible adenoma of either lobe of the thyroid should render a

diagnosis of intrathoracic goiter. Large intrathoracic goiters may remain symptomless owing to the capaciousness of the thoracic cavity, the relative mobility of its contents and the faculty of its contents to be readily displaced, yet not actually being compressed. The latter, however, is not true of the recurrent laryngeal nerve, for displacement of the large arterial trunks usually exerts traction, thereby causing a total or partial paralysis.[11] The pressure effect upon the recurrent laryngeal nerve is slow in onset, and the cords accommodate themselves, so that a laryngoscopic examination is essential to detect the paresis. Hoarseness was present in 10 per cent of the cases. Pain is never present unless the tumor is malignant, but a sense of fulness in the upper chest is a very frequent symptom.

Percussion as an aid to diagnosis is at best unreliable; definite, positive findings being ascertained by means of the fluoroscope, Roentgen ray and bronchoscope. Hunermann does not advocate the use of bronchoscopy, owing to the danger entailed, and claims that it seldom gives one an idea of the position, size and type of tumor dealt with. Even with the Roentgen ray errors are possible, but only as regards the type or pathology of the mass present. An intelligent and complete examination, including the fluoroscope and Roentgen ray of all patients presenting symptoms of socalled "idiopathic" auricular fibrillation, severe asthma, persistent cough, and aneurysm would prevent such diagnosis being made.

Roentgan ray examination frequently reveals the trachea to be compressed and deviated from the normal. At times the Roentgen ray findings are confusing. It is usual to mistake an intrathoracic goiter for a sacculated aneurysm of the ascending arch of the aorta which it may simulate very closely. Fluoroscopy is a great help in differentiating between the two. If the shadow noted moves synchronously with the respiratory movements and should it definitely lack expansile characteristics, the diagnosis of aneurysm is immediately eliminated. Occasionally an aneurysm may lack this characteristic because of firm clots within it. In such cases Roentgen ray plates when carefully examined may show a distinct line of demarkation between the shadow and the aorta. An oft confusing shadow is that of a persistent thymus. The latter is infrequently seen in adults; it is as a rule bilateral, and has a more hazy and indistinct outline than other thoracic growths. It does not attain the size of an intrathoracic goiter, and rarely, except in infants, gives rise to severe signs and symptoms of compression.

Hodgkin's disease and lymphosarcoma should seldom cause difficulties in the differential diagnosis. They are situated at the lung hilus and spread peripherally in a butterfly fashion. They seldom have as distinct a margin as intrathoracic goiters, are usually bilateral and frequently infiltrate the adjacent tissues. The progress of the latter diseases are more rapid and always downward.

Finally, all tumor masses in the upper mediastinum in close proximity to the aorta should always arouse suspicion of retrosternal struma, expecially if on Roentgen ray examination the shadows have a sharp, distinct and roundish outline, and do not pulsate when viewed under the fluoroscope.

Case Reports. CASE I.—R. H., female, aged fifty-five years, Russian, was admitted to the Montefiore Hospital, with the following complaints: inability to walk, irritability, anxiety, insomnia, headaches and fainting spells. She also complained of dyspnea on exertion. Her family and past history are irrelevant. The patient presented the following positive findings: Her face was flushed. There was a moderate exophthalmos plus von Graeff's sign. The thyroid gland was enlarged, especially to the left. The superficial cervical veins and those over the sternum were enlarged, tortuous and engorged. The heart was moderately enlarged to the left. The sounds were feeble but no murmurs were audible. There was a wide area of dulness beyond the manubrium sterni on either side, with tubular breath sounds over the right upper lobe. The diagnosis was that of hyperthyroidism, aneurysm of the aorta or mediastinal tumor. The roentgenologist's report was that of aneurysm of the arch of the aorta. Exactly one year later the Roentgen ray findings remained the same. No fluoroscopic examination had ever been made. The patient died and autopsy revealed the following: Advanced generalized arteriosclerosis, hypertrophy of the left ventricle, large adenoma of the thyroid extending into the upper anterior mediastinum with compression of the surrounding structures. There was also degeneration of the caudate and lenticular nucleus, and a small adenoma of the adrenal.

Cross section of the thyroid showed a structure of average consistency situated between the two lobes as an isthmus composed of a large globular mass, 5 by $3\frac{1}{2}$ by $2\frac{3}{4}$ cm. in size. The consistency of this mass was greater than that of the thyroid, and in some portions it was calcified to a stony hardness. On cross section this isthmus had an irregular architecture, in some places a translucent fleshy appearance. There were small hemorrhages here and there, with islands of colloid. The appearance was that of a fetal adenoma, showing areas of degeneration and calcification. In addition to this globular mass, there were two other globular masses, one situated on the right side $6\frac{1}{2}$ by 5 by $\frac{3}{4}$ cm., and on the left side, a mass 8 by 6 by $4\frac{1}{2}$ cm. On section these masses were similar to the mass of the isthmus, and like it were enclosed in a thin fibrous capsule. These two masses were attached to the isthmus and to the right and left lobes of the thyroid respectively by fibrous strands adherent to the capsule.

Before removal from the body these masses occupied the same position in the thorax, corresponding to the two previous Roentgen ray shadows.

Sections from various portions showed microscopically, a picture of fetal adenoma with atrophy and replacement fibrosis.

CASE II.—S. O'M., male, aged thirty-eight years, was born in Ireland. He complained of fatigue and frequent attacks of palpitation and "nervousness." His family and past personal history were negative. His present illness dated back about a year. Recently, he gradually lost weight, and with this there were some precordial pains, with a sensation of fulness in the upper mediastinum. This fullness was slight. At times it would increase and induce spasms of coughing. Aside from the above his entire personal history was negative. Physical examination revealed the following positive findings: The patient was a lean enteroptotic individual. There was an overactive heart, slight tremors of the hands, and a generalized hyper-reflexia. Otherwise, physical examination was entirely normal. Fluoroscopic examination presented a shadow lying to the right of the ascending arch of the aorta. It was the size of a lemon and moved with each pulsation of the aorta, but distinctly lacked the expansile character to its movement. The movement was merely due to the transmission of the aortic pulsation. Its outline was sharp and distinctly circular and contained many calcified masses within its body. There also appeared to be discreet calcified masses ascending toward the neck. A teleoroentgenogram showed that the mass was distinct from that of the aorta which it fairly straddled. The heart was of the dropped type and rather small. The electrocardiogram, except for a left ventricular preponderance, showed normal deflections.

CASE III.—J. S., aged fifty years, Russian, female, complained of shortness of breath and palpitation. The history of the present illness began two years ago with palpitation and dyspnea on exertion. Her past personal history was otherwise normal. The physical findings were entirely negative except for slight increase in cardiac dullness to the left and an irregularity in the rhythmicity of the heart sounds (auricular fibrillation). Roentgen ray revealed a shadow apparently arising from the arch of the aorta. This was previously diagnosed as an aneurysm. The heart was enlarged to the left but the aorta was normal. Fluoroscopic examination showed that the shadow lacked expansile pulsation and was distinct from the shadow of the aorta, as evidenced by the Roentgen ray photograph. The electrocardiogram revealed a typical picture of auricular fibrillation with occasional extrasystoles, probably arising in the right ventricle.

The two latter cases were previously examined by Roentgen ray, and diagnosed as aneurysm, owing to the masses observed within the chest. Careful fluoroscopic examination, and good Roentgen ray plates would have avoided such mistakes. In the

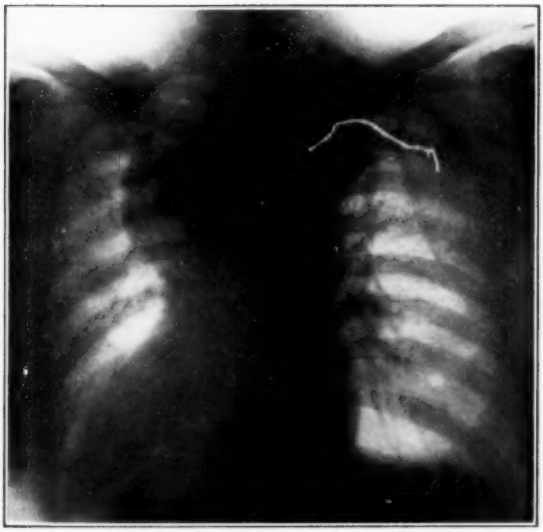

FIG. 1.—Case I. Roentgenogram of chest showing the large intrathoracic shadow. The denser structure of arch of aorta is distinct.

FIG. 2.—Case I. Specimen of thyroid adenomata removed at autopsy, showing the close proximity to the aorta.

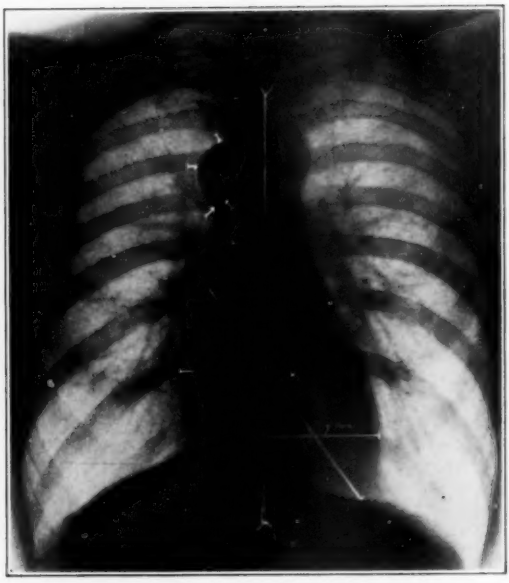

FIG. 3.—Case II. Teleroentgenogram. The shadow to the right of the aorta resembles a sacculated aneurysm for which it was mistaken. It is an example of an aberrant intrathoracic goiter with areas of calcification.

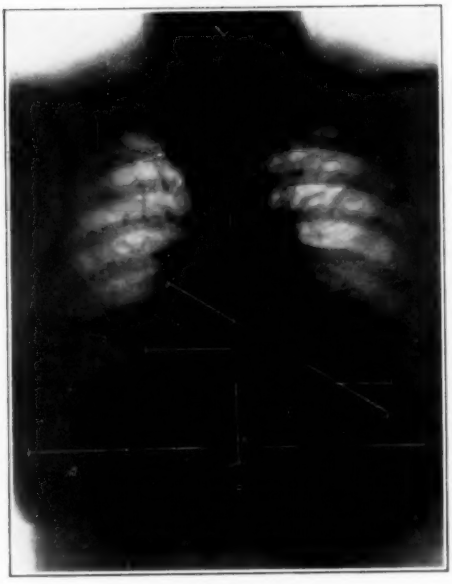

FIG. 4

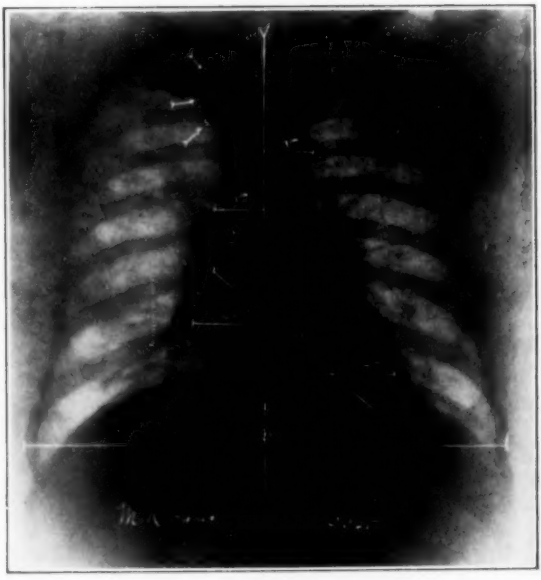

FIG. 5

FIGS. 4 and 5.—Cases III and IV. Teleroentgenograms. The shadows are alike and are situated behind the right clavicular sternal region. This is a very common sight for retrosternal goiters.

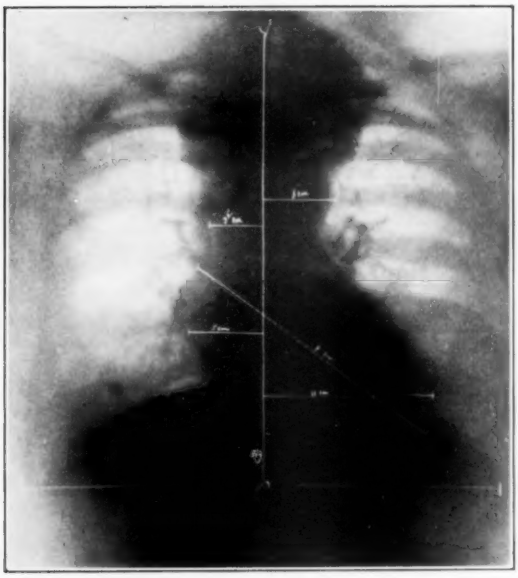

FIG. 6.—CASE VI.—Teleroentgenogram. A large retrosternal mass gave rise to marked symptoms and signs of mediastinal compression.

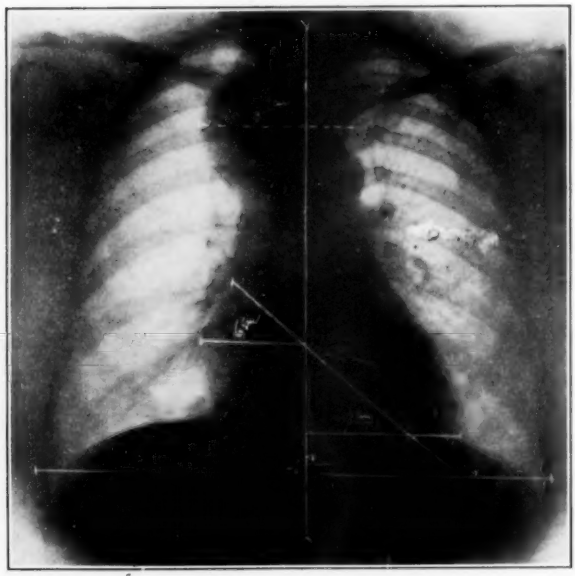

FIG. 7.—Case VII.—Teleroentgenogram. Large mass in about same situation as Case II, and giving rise to no symptoms.

former an expansile pulsation should be sought for in order to render a diagnosis of aneurysm, and in the latter, a mass distinct from that of the aorta should be detected so as to eliminate a diagnosis of the same. Case II, presenting an auricular fibrillation, was given quinidin with no effect, apparently due to the fact that the thyroid was the agent in its causation. The patient has been seen a number of times after taking minute doses of thyroid and has improved remarkably.

Case IV.—M. L., male, aged forty-one years, Austrian, auctioneer, complained of pains in the precordium for one year. This began with a "nervous breakdown" following business worries. Pain was exaggerated by eating and exertion and lasted for an hour or more. There was no dyspnea or other cardiopulmonary symptom. The entire physical examination was negative except for a generalized hyper-reflexia. Fluoroscopic examination revealed a small well-defined shadow below the right sternoclavicular junction which moved with respiration. It was about the size of a small lemon. Its character, size and position were well shown by the teleroentgenogram. Iodin in minute doses given intermittently resulted in complete recession of all his subjective symptoms.

Case V.—E. R., male, German, manufacturer, aged fifty-one years, complained of pain of an anginoid character, with typical radiation. There was pain in the precordium for the past six months following eating and exertion. His father died of angina pectoris, otherwise his family and personal histories were negative. Physically, he presented a systolic murmur over the apex. There was a trace of sugar in the urine. The Roentgen ray picture was identical with that of case IV (M. L.). The electrocardiogram showed evidence of a left ventricular preponderance.

Case VI.—R. de S., aged forty years, female, Italian, complained of shortness of breath, with swelling of hands and face. Her family and past histories were negative. Her present illness began a year and a half ago. Her hands and the veins of the upper extremities became visibly swollen. Palpitation became severe in the last three weeks. Dyspnea was very distressing on the least exertion. Examination revealed a large distended mass of veins in the neck and both upper extremities, with some cyanosis of both hands. On placing finger in episternal notch a firm elastic mass was felt. There was a distinct increase of dulness on percussion over the manubrium sterni, and a rough systolic murmur was audible over the mitral area, but the heart was not found to be enlarged. The patient was three and a half months pregnant. The urine showed a heavy trace of albumin, but no casts or erythrocytes were present. A teleroentgenogram revealed a large mass behind the

manubrium reaching further toward the left than the right. It was distinct from the shadow of the aorta and was pulseless under fluoroscopic view. The heart was slightly enlarged and the aorta somewhat dilated.

This patient was originally sent as a case of mediastinal new growth. However, this was apparently a retrosternal thyroid, which, under the stress of pregnancy, had undergone hyperplastic change. Thyroid was given in a dose of 0.0065 gm. (gr. $\frac{1}{10}$) three times a day. The improvement in signs and symptoms was remarkable, and she was able to give birth to her child at term without difficulty. In a recent communication with her physician it was learned that she had been delivered successfully of another child.*

Case VII.—B. S., a female, aged forty-six years, was born in Germany. Her condition was accidently discovered while undergoing a gastro-intestinal examination. There was a shadow seen, the size of a large orange behind the upper portion of the sternum, more to the right than to the left. It extended into the neck and could be manually felt as a distinctly nodular, elastic, firm mass. The heart and aorta were somewhat enlarged. This patient has been frequently observed since the original examination and is in good health. The mass has not enlarged and no treatment has been instituted. She came from a region where goiters are prevalent, and her mother also, has a large goiter.

This is an instance of a large thyroid mass situated in the upper mediastinum, giving rise to no signs of compression in spite of its location and diameters.

Treatment. Very little can be said about the treatment as many of these cases are symptomless and may remain benign for many years. In 2 of our cases, minute doses of thyroid seemingly caused recession and great symptomatic improvement. The small doses of iodides as advocated by Marine for the prevention of goiters in endemic regions would also undoubtedly control the incidence of substernal goiter. Where symptoms of mediastinal compression are severe, we have recourse to two methods of treatment. The first is deep roentgen therapy, which has been beneficial in a few reported cases, and second, surgical interference when the former fails. The latter should be resorted to only in those cases where the symptoms are grave and failed to respond previously to conservative methods of treatment.

* It has been our good fortune to reëxamine patient R. de S., on November 23, 1925. Her general condition is excellent. There remains a slight residua of distended veins of her left arm and some signs of hypothyroidism. The teleroentgenogram shows a difference of 2 cms. in the size of the shadow in the transverse diameter, *i. e.*, 12 cms. on previous examination, and 10 centimeters to date.

Conclusions. 1. Substernal thyroid is more frequent than is usually believed.

2. Any shadow in the upper mediastinum, which shows a distinct line of demarkation, and is separate from the aorta, is usually a retrosternal goiter.

3. Fluoroscopic examination reveals the absence of expansile characteristics.

4. The mass moves with the trachea during respiration.

5. A visible goiter, plus signs of compression; or signs of compression, plus thyrotoxic symptoms, are indicative of a substernal goiter.

6. Auricular fibrillation associated with indications of a mass behind the manubrium sterni points toward the existence of a substernal thyroid.

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PROGNOSIS IN EXOPHTHALMIC GOITER.

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This report is based on the findings in 100 cases of Graves' disease seen by the writer during the past six years. Being purely a clinical study, consideration of pathology in those cases where pathological material was obtained will be reserved for a future communication.

Definition. Neither Parry, when he described 8 cases one hundred years ago, nor Graves, who described 4 cases ninety years ago, gave a definition of this interesting disease. Since confusion often arises through failure to define terms, it seems advisable to

state what I mean by exophthalmic goiter thus: A constitutional disease of unknown etiology, exhibiting as major characteristics tachycardia, elevated basal metabolic rate, goiter and exophthalmos, these being accompanied in most cases by one or more of the following: Tremor, nervousness, insomnia, weight loss, sweating, pigmentation, vomiting, diarrhea and mental aberration. This definition excludes toxic adenoma, though tachycardia and increased metabolic rate are constantly present in both conditions.

Clinical Features. The firmly established and universally recognized clinical points in this disease may be summarized as follows: It occurs at all ages and in all parts of the world, though its incidence seems to be greater in goiter districts. It is about nine times more frequent in females than in males. It is prone to run a cyclic course with remissions and recrudescences,[1, 2, 3] and has a tendency toward chronicity, though it frequently results in spontaneous recovery, which facts render the evaluation of therapeutic procedures rather difficult. It presents atypical forms and there is an irreducible minimum of mortality.

The most constant feature of this disease, without which the diagnosis is never justified, is an elevated basal metabolic rate. When accurately determined it furnishes a reliable objective, quantitative estimate of the severity of the disease. Utilization of this diagnostic aid was a constant feature in the study of all cases in this series, a total of over four hundred determinations being made on 100 patients.

Data. It was deemed advisable to consider separately the cases of those patients who had submitted to surgical intervention prior to coming under my observation. In addition to illustrating a frequent result of one form of treatment, they possess in common chronicity and similar prognostic and therapeutic features. The cases in which prior surgery was not a factor were arbitrarily subdivided into two groups—one the typical, the other the atypical cases.

The first group comprises 56 typical cases, with basal metabolic rates from +22 to 112 and an average of +54, as shown in Table I. There were 11 males and 45 females, the relatively high percentage of men being due to the fact that the U. S. Veterans' Bureau furnished a number of men in the series. Though the main features are given in Table I, such a mode of presentation is inadequate to bring out all that is to be learned from such a series. Of the 6 deaths, 4 occurred in patients who were operated upon. These will be discussed later under the head of "surgery." The other 2 were cardiac deaths in patients who were fibrillating since first coming under observation. One of these was a man, aged fifty-seven years, who, according to his history, had suffered from this disease since the San Francisco earthquake in 1906. Three of the cases in this group have been reported in detail elsewhere.[4]

TABLE I.—EXOPHTHALMIC GOITER. GROUP I (56 CASES).

Sex.	Age	Duration of symptoms before M.D. was consulted, years.			Basal Metabolic rates.*						Treatment.							Result.				
					First.			Last.														
	Ave.	Av.	Max.	Min.	Av.	Max.	Min.	Av.	Max.	Min.	Surgery.	Roentgen-ray.	Iodin.	Rem. foc. infs.	Ovarian extr.	Thyroid extr.	Salvarsan.	Cured.	Improved.	Not improved.	Died.	No follow up
Female (45)	37	1½	7	1 mo.	55	112	22	17	60	−16	10	35	14	2	1	2	..	20	18	2	5	1
Male (11)	38½	3¼	15	1 mo.	53	70	25	27	60	3	4	5	2	2	—	0	1	3	5	1	1	0
Total (56)	37¼	2	..	....	54½	....	..	20	..	....	14	40	16	4	1	2	1	23	23	3	6	1

ATYPICAL EXOPHTHALMIC GOITER. GROUP II (19 CASES).

Female (17)	32	1½	4	1	25	65	−18†	14	29	5	1	9	3	2	0	0	0	13	3	..	1	
Male (2)	36	..	..	..	30	40	21	16	23	9	0	2	0	0	0	0	0	..	1	..	1††	
Total (19)	32½	..	..	..	25½	..	..	14¼	..	..	1	11	3	2	0	0	0	13	4	..	2	

* The signs of all B. M. R. readings are plus unless indicated as minus. (Tables I and II).
† At an examination nineteen months later this patient's B. M. R. was +15 per cent. †† "Lost at sea."

The second group consists of 19 mild and atypical cases, summarized also in Table I. The outstanding symptoms presented by the patients in this group were: Tachycardia, nervousness and loss of weight. None of these had exophthalmos nor the classical signs of exophthalmic goiter, though many had slight enlargement of the thyroid gland. All had elevations of the basal metabolic rate varying from +13 to +65 before treatment. Since none of these patients had exophthalmos and only a few had goiter, the appellation, "exophthalmic goiter," might be disputed. With persistent elevation of the basal metabolic rate and many of the other classical signs of this disease, without other evident cause for the condition, one must make the diagnosis of exophthalmic goiter.

None of these cases fell under the classification of effort syndrome or irritable heart, for they all had elevation of the basal metabolic rate and, furthermore, the outcome in most of these cases was cure in from three months to a year. Some of this group ran the typical course of remissions and recrudescences so characteristic of this disease, those with the higher rates tending to run a longer course and more nearly approaching the typical case of the first group. In fact, the division line between the two groups is purely arbitrary for the 75 cases could be arranged in a continuous series beginning with the severe cases, most of which had the fully developed picture, and ending with the mild cases which were for the most part atypical. In the atypical, or mild cases, the prognosis is favorable for complete recovery under ordinary symptomatic treatment, neither roentgenotherapy nor surgery being required, though the former was used in 11 of these cases and one thyroidectomy was performed on a patient whose metabolic rate was only +13.

There was 1 death in this group, a physician's wife, aged thirty-six years, who had a persistent hypertension (systolic, 186 to 222; diastolic, 150 to 160), taken always under basal conditions while resting between two determinations of her oxygen consumption. The basal metabolic rate ranged from +19 to +41. There were six estimations made between March 28, 1923, and April 23, 1924, during which period she had a remission of her symptoms, though she died about six months after the last recorded date. This patient fits the description of 5 cases recently reported by Boas and Shapiro,[5] all of whom had hypertension and elevation of the metabolic rate. In view of the frequency of hypertension, I do not believe that there is sufficient evidence to justify the hypothesis that these cases represent more than the chance association of two unrelated conditions.

Group III consits of 25 patients whose thyroids had been operated upon before coming under my observation. Their basal metabolic all rates varied from —7 to +80, as shown in Table II. They all presented some of the signs or symptoms for which thyroidectomy

had been performed, and for which they sought further relief. That they originally had Graves' disease was determined from the evident persistence of some of the classical features or statements from the operator or patient that this disease existed prior to operation. Four of these cases have already been reported in detail.[4, 6]

The first fact demonstrated by this group is that thyroidectomy (subtotal in many of the cases) does not always produce a cure, although it usually results in some improvement. The second evident fact is the chronicity of this disease in some patients. It is assumed that persistence of the condition is in spite of surgery, not because of it, for it seems to be true that in some cases the signs and symptoms become chronic regardless of any or all treatment. Iodin was found to be the most potent therapeutic weapon in treating the patients in this group.

Surgery. In addition to the 25 patients of Group III, 16 patients of Groups I and II submitted to surgical intervention, all being thyroidectomized, except 1 who had double ligation. Five of these 16 died; 3 in acute "thyroid crises;" 2, twenty-four and forty-eight hours after operation. One died three months after double ligation while waiting to reach a condition favorable for thyroidectomy. The fifth succumbed five months after a second thyroidectomy which reduced him to a state of myxedema and tetany. The 16 operations represent the work of eight surgeons, all of whom are skilled operators, yet the mortality rate in this group is 31 per cent. Kessel and Hyman[7] report an immediate operative mortality rate of 9.3 per cent in 43 subtotal thyroidectomies. These figures suggest the probability that surgical treatment of exophthalmic goiter throughout the whole United States is attended by a mortality rate which is several times the very low rates reported from a few of the best thyroid clinics in this country.

My experience with surgery in exophthalmic goiter, both from the standpoint of mortality rate and results, is such as to dampen any enthusiasm I might otherwise have for this form of therapy. Perhaps my experience has been peculiarly unfortunate. Nevertheless I am moved to report the 25 cases previously operated on, which I regard as surgical failures, because they constitute a type of case frequently encountered but seldom reported. While recognizing the fact that surgical measures failed to restore these patients to health, it is my belief that they belong to the class of chronic cases which are never cured. Some, perhaps many of them, were medical failures before they became surgical failures. No criticism of the surgery is offered for some of these patients had journeyed to the best thyroid clinics in the country, while others had expert surgery in this vicinity (Table II).

TABLE II.—PRIOR SURGICAL TREATMENT. GROUP III (25 CASES).

No.	Age.	Sex.	Operation.			Major presenting complaint.	B. M. R.				Treatment.	Result.
							First.		Last.			
			Date.	Place.	Type.		Date.		Date.			
1	40	F.	2/1918	S. F.	Lobectomy	Weight loss	3/22/22	74	9/25/23	33	Roentgen-ray, iodin	Moderate improvement.
2	30	F.	1920	Colorado	Double lobectomy	Fast heart, nervous	11/ 4/22	11	.....	..	.....	No follow up.
3	35	M.	4/16/21	S. F.	Partial thyroidectomy	Weight loss, nervous	12/15/21	38	4/22/22	−9	Total thyroidectomy	Death.
4	38	F.	11/15/19	S. F.	Partial thyroidectomy	Fast heart, nervous	9/19/23	80	5/ 5/24	4	Roentgen-ray, iodin	Accidental death.
5	26	F.	1917	San Jose, Calif.	Partial thyroidectomy	Fast heart, weakness	10/27/20	24	8/30/24	5	Iodin, roentgen ray	Cured.
6	58	F.	1912	S. F.	Lobectomy	Fast heart, headache	11/27/21	−6	3/25/25	3	Rest	Improved.
7	53	F.	4/22 6/22	S. F. S. F.	Ligations, thyroidectomy	Nervous	11/11/22	33	7/10/25	13	Roentgen-ray, iodin	Slightly improved.
8	46	M.	1912 1913	Rochester, Minn.	3 ligations, hot water injections. Two lobectomies	Weakness, fast heart	9/27/22	49	6/ 4/24	23	Roentgen-ray in 1913, iodin 1924	Improved.
9	36	M.	2/20 5/20	S. F.	Ligations, subtotal thyroidectomy	Weight loss, fast heart	3/17/25	42	6/13/25	86	Roentgen-ray, iodin	Worse.
10	42	F.	1914	S. F.	Lobectomy	Weight loss	8/20/21	16	9/27/24	65	Iodin, induced menopause	Worse.

11	33	M.	11/20	S. F.	Lobectomy	Weight loss	10/10/24	40	12/ 2/22	47	Roentgen-ray	No change.
12	32	M.	1919	S. F.	Lobectomy	Fast heart, nervous	7/18/22	29	.....	..	.....	U. S. Vet's., rating 50 per cent.
13	36	F.	1914	S. F.	Thyroidectomy	Fast heart, nausea	8/11/22	3	.....	..	Roentgen-ray '16, ovarian ex.	Improved.
14	35	F.	3/24/21	S. F.	Subtotal thyroidectomy	Weakness, fast heart	6/14/21	16	7/ 8/21	−2	Roentgen-ray	Improved.
15	29	F.	4/1920	Minnesota City–?	Partial thyroidectomy	Fast heart, weight loss	3/31/24	−1	4/15/24	16	Iodin	Improved.
16	29	F.	1920	S. F.	Lobectomy	Fatigue	10/11/21	26	11/23/21	−4	Roentgen-ray	Improved.
17	32	M.	4/1920	U.S.P.H.S.	Lobectomy	Fast heart	6/12/22	0	.....	..	.....	Cured.
18	34	F.	11/1920	S. F.	Subtotal thyroidectomy	Fast heart, nervous	3/ 2/21	14	.....	..	.....	Suicide (?)
19	43	F.	1914	Rochester, Minn.	Partial thyroidectomy	Nervous	12/16/22	14	5/23/23	36	.....	No change.
20	40	F.	9/1915	New York	Partial thyroidectomy	Nervous	3/ 7/23	1	.....	..	Roentgen-ray	Improved.
21	51	F.	1911	Cleveland (Crile)	?	Nervous fears	8/31/23	−2	.....	..	Thyroid, ovarian ex.	No change.
22	36	M.	1917	Chicago	Thyroidectomy	Cough, abdominal pain	11/28/23	16	.....	..	.....	No follow up.
23	28	M.	1/1922	?	Ligation	.....	8/1922	20	1/13/23	4	.....	No follow up.
24	23	F.	8/26/21	S. F.	Right lobe and isthmus	Fast heart, nervous	7/15/22	−7	.....	..	.....	Improved.
25	29	F.	1914	Rochester, Minn.	Thyroidectomy	.....	9/27/24	7	.....	..	Iodin, ovarian ex.	Improved.

Prognosis. Search of the literature fails to yield much information regarding prognosis in exophthalmic goiter, nearly all statements being colored by the writer's theory of etiology or more particularly the result of the form of therapy administered. The most helpful work elucidating this point recently was that reported by Kessel, Hyman and Lande.[8] They observed the course of this disease in a series of patients who were given only symptomatic therapy and reported results which vary but little from those obtained when elaborate and detailed therapeutic procedures were followed.

Some rather extensive and illuminating figures upon which one may base some ideas of prognosis were published by Hale-White[9] in 1910. He reported 226 cases, including all of those (169) admitted to Guy's Hospital from 1888 to 1907 and 57 private patients seen from 1894 to 1909. Exclusive of 3 patients, who died directly from operative procedures, the immediate mortality rate among the other 166 hospital cases was 10.7 per cent. In the whole series 11 patients were operated upon with 4 immediate deaths. He classified 65 per cent of the whole number as "mild or average," 24 per cent "severe," and 11 per cent "very severe," and makes the interesting observation that the ultimate outcome of the case did not depend on the severity of the disease when the patient was first seen for some milder ones ran long courses and were never cured, while 8 hospital and 17 private cases grouped as severe or very severe have done well. He believes that the social status is a very important factor, because the percentage of recoveries was much higher among the private than among the hospital cases, though both groups were of equal severity, most of the private cases being seen in consultation. Exclusive of 22 deaths while still under observation, there were traceable 110 patients of whom 70 per cent "got quite well," 24 per cent "were much better" and 6 per cent "were better in some respect or other." Actuarial calculation showed that the death rate for patients with this disease is about twice that of normal females of the same age, but as the latter is not high for this age (thirty to forty-five years), the mortality among patients with exophthalmic goiter is not excessive. The ratio of males and females in this series was 1 to 11.

Hale-White's work is very valuable, it seems to me, as it furnishes data on the later course of the disease. Though his patients received more symptomatic treatment than did those of Kessel and others, still it is probable that the bed rest was the most valuable, though it probably did not affect the course of the disease, as is sometimes possible by iodin, Roentgen ray or surgery. The elapsed time is quite sufficient to demonstrate that most patients recover from Graves' disease, and that the mortality rate is not high.

In the Bradshaw Lecture for 1916 Hector Mackenzie[10] sums up

prognosis in exophthalmic goiter as follows: "There is reason to believe that in about 25 per cent of the cases death results from the disease, and that under ordinary medical treatment in about 50 per cent more or less complete recovery will eventually take place, while in the remainder the disease continues in a chronic form during life."

From a survey of this series one gathers the following impressions regarding prognosis, which are in accord with the findings of the authors just cited: Some cases run a course to spontaneous recovery, some will die in spite of all therapy and some because of it. The chief concern with the first class is to avoid therapeutic procedures which will bring about a fatal termination. The mortality rate in this series is 11 per cent. Ten of the deaths have been discussed already. The eleventh was due to veronal poisoning, probably suicidal. Exclusive of 4 deaths directly due to surgery, the mortality rate is 7.3 per cent, and further deducting 3 accidental deaths it is 4.3 per cent.

Thirty-eight per cent seem to be cured and about 21 per cent are sufficiently improved as to be restored to full social and economic usefulness. The remaining 30 per cent, which includes 23 of the 25 patients previously operated upon, will be sufferers from the disease or its sequelæ the remainder of their lives. The tendency for this disease to become chronic in certain instances is a feature which has not been sufficiently stressed. However, recognition and emphasis of this, and also the fact that this disease runs a fairly characteristic course and often ends in spontaneous recovery, must not be interpreted as indicating an attitude of therapeutic nihilism. Some writers, Leonard Williams for example, are inclined to doubt "Whether in pronounced cases recovery is ever complete." The chronicity in many cases lends support to that opinion. But what constitutes a pronounced case is not always easy to determine. The metabolic rate is the most valuable aid, but patients with very high rates may run a short course to satisfactory recovery. Those conditions which are universally conceded to augur ill for the patient are gastrointestinal symptoms in particular, and mental aberration, which is often permanent.

The acute fulminating cases with high metabolic rates, hyperthermia, dysentery, vomiting and mania, are fortunately rare. I have never seen one, but should I be called to express an opinion upon such a case I should consider the prognosis unfavorable for recovery and anticipate an early exitus.

Sex. As to sex in relation to prognosis, this survey seems to show that males are more resistant to treatment of all kinds, and there is greater likelihood of the disease becoming chronic than in females. The U. S. Mortality Statistics for the twelve years from 1910 to 1921, inclusive, report 11,212 females and 1532 males as having died from exophthalmic goiter. This is a ratio of 1 male

to 7.32 females, which is a slightly higher percentage of males than is reported in most series in the literature. This might be taken to indicate a higher mortality rate among males. There were 20 males in this series, of whom 3 are dead. One is reported simply as "lost at sea;" 1 is the already-mentioned long-standing case with auricular fibrillation and death from cardiac failure; the third was a beneficiary of the Veterans' Bureau, who died of tetany and myxedema following a second thyroidectomy. Of the remaining 17 men only 3 can be classified as cured.

Age. Age does not seem to be such an important factor as some writers believe. The average age in all three groups of this series is about thirty-seven years for both sexes. The youngest patient was a girl, aged thirteen years, who presented quite a typical picture, though the metabolic rate was never more than +22. She has entirely recovered one year after thyroidectomy, a procedure which I believed was unnecessary in her case, as her trouble seemed to be associated with the onset of menstruation, and she improved and gained 20 pounds in two months after iodin therapy. The oldest patient was a woman, aged sixty-four years, whose first basal metabolic rate was +78. This had dropped to +11 twenty-three months later, at which time she was encountered in a hospital corridor working as a maid. One other patient, a woman, aged sixty years, made a complete recovery in a year. Both these patients received roentgenotherapy.

Menopause and Pregnancy. It has been stated that women who developed Graves' disease at the menopause have a prognosis unfavorable for recovery. That has not been my experience, though I have seen a number of patients suffering from this disease at the time of the climacteric. Causing cessation of menstruation by roentgenotherapy is often a therapeutic measure of great benefit in this type, which fact suggests that the signs of thyroid disturbance are a part of the glandular readjustment at this time of life.

Pregnancy is a serious event in this disease, often precipitating a crisis, and many cases have their onset at this time. One case of this series illustrating this point has been reported previously.[6] It is questionable if a woman who has had this disease should become pregnant. No better test of cure exists than to go successfully through a pregnancy.

Time Element. An interesting point revealed in the study of the individual case histories in this series, and one of some significance, is the long duration of symptoms before medical aid is sought. Fortunately this is not an incapacitating disease; in fact, in the early stages the patient feels exhilarated. As a consequence, patients frequently do not seek aid for many months or years. A study of this point was made, and it was discovered that the average duration of symptoms before visiting a physician was one year and

two months in those patients classified as "cured" and two years and six months in those patients who can only be called "improved."

The former seem to be acute cases with fairly well-defined onset, rapid progress and prompt recovery. These patients may be very ill, with metabolic rates as high as +80, and lose considerable weight. The thyroid is often only slightly enlarged. The prognosis is favorable for recovery under any intelligent treatment.

The chronic type has a more insidious onset, often preceded for years by thyroid enlargement. One might think that they were acute cases which did not receive treatment and had become chronic, but I do not believe this to be a fact, for many acute cases run a short course to spontaneous recovery without treatment, and this chronic type of case continues resistant to therapy even when seen fairly early in its course.

Causes of Death. Death in exophthalmic goiter is generally by one of two routes: First, acute crisis, which may terminate a case only a few days after its onset, or it may develop without apparent cause in a long-standing case. Such an exitus was a too frequent occurrence following thyroidectomy in the days prior to preoperative preparation by saturation with iodin. Three of the surgical deaths in this series were of this type, the pulse rates going to 176 to 182 and temperatures to 41.2° C. just before death.

The second manner of demise is by cardiac failure, which is most often preceded for many years by auricular fibrillation. It is unnecessary to dwell here upon this effect of the disease, for Kerr and Hensel,[11] Levine and Sturgis,[12] Hamilton,[13] Dunhill, Fraser and Stott[14] have all written recently upon the cardiac complications and sequelæ of this disease. Damshek[15] reviewed the subject completely last year and compiled a bibliography of eighty-four references.

Cardiovascular Complications. Six patients in this series had fibrillation. Three are dead, 1, however, being killed in a street accident. Of the other 3, 1 was still fibrillating four years after discharge, though she had apparently recovered from the Graves' syndrome, and was not decompensated. One did not reply to my questionnaire and the sixth is doing well. Willius, of the Mayo Clinic, states that 7 per cent of patients with exophthalmic goiter go into auricular fibrillation.

A more frequent type of irregularity encountered in this group was ventricular premature systoles, which seem to occur in nearly all patients with Graves' disease at some time in its course. They do not materially affect prognosis unless accompanied by other signs of myocardial change.

Of more value prognostically is the blood pressure. Leaving out of consideration the atypical cases with marked hypertension already mentioned, I believe that patients with high systolic and relatively high diastolic pressures do not recover so quickly as those

with lower pressures. It has been previously noted elsewhere[16] that with increased oxygen consumption a wider pulse pressure is the rule. This widening of the pulse pressure is generally accomplished by lowering the diastolic and elevating the systolic pressures. But in patients who appear to have difficulty in making this seemingly physiological adaptation the course of the disease is not so smooth or so short. I recall one patient in particular, a young woman, aged twenty-three years, who has now entirely recovered, but who ran a very obstinate course and had blood-pressure readings which were constantly high. Troell,[17] a Swedish worker, has made some studies on blood pressure in this disease, and believes that marked deviations from the normal relationships which exist between systolic, diastolic and pulse pressure are of prognostic value.

The frequent, perhaps constant, occurrence of damage to the cardiovascular system in this disease presents a serious problem to the clinician and to prevent this damage is his chief concern in endeavoring to shorten the course of the disease as much as possible. Prevention of cardiac damage is the strongest argument for surgical intervention, and if this desirable end were more frequently accomplished some of the unfavorable aspects of this therapeutic procedure would be counterbalanced.

Conclusions. 1. Acute cases of exophthalmic goiter with well-defined onset offer a more favorable prognosis for recovery than those with insidious onset and symptoms existing for several years before seeking medical advice.

2. The height of the basal metabolic rate offers only slight assistance in estimating the prognosis.

3. Males with exophthalmic goiter seem more resistant to treatment and are more apt to become chronic sufferers than are females.

4. Subtotal thyroidectomy nearly always produces a remission of the disease if the patient survives the operation, but it does not constitute a cure.

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TOTAL THYROIDECTOMY IN THYROTOXICOSIS OF THE EXOPHTHALMIC TYPE. A PRELIMINARY REPORT.

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(From the Stanford University Medical School and Hospital.)

From the observation extending over a number of years of a large number of patients suffering from thyrotoxicosis of the exophthalmic type treated by the usual surgical measures we were impressed that the recovery of many was decidedly incomplete. We also noted that the greater the amount of gland removed at operation the more complete the cure of the patient.

We argued that in this condition the entire thyroid gland is diseased and should be removed. For a diseased gland could then be substituted the extract of a normal gland. We decided therefore upon complete removal of the thyroid in thyrotoxicosis of this type and administration of thyroid extract.

We have also observed in a number of cases that the greater the amount of thyroid gland removed at operation the less the reaction, the shorter the period of convalescence and the sooner the patient was able to resume his occupation. More important still these individuals did not relapse.

Each of the individuals making up this series had been under treatment for from one to eight years, was suffering, and was absolutely incapacitated from useful pursuits during these periods.

In addition each was classed as incurable and was considered a poor operative risk.

Ten patients form the basis for this preliminary report and of these, 7 had been under continuous medical supervision including the usual methods indicated by that term from one to eight years. Each of these 7 had received numerous Roentgen ray treatments, 2 as many as sixty.

To each patient, before subjecting him to a total thyroidectomy, our object was carefully explained as was the fact that they would have to take a certain daily amount of thyroid preparation for the remainder of their lives. No difficulty was experienced in obtaining the patient's consent as all of this group of individuals were hopeless invalids.

The operation consisted in removing the entire thyroid gland, the safety of the parathyroids and recurrent laryngeal nerves being insured by shaving the posterior portion of each lateral lobe as close to the capsule as possible. All but 2 patients received iodin both before and after the operation.

Case Reports. CASE I.—D. H., aged fifty-six years, male, with thyrotoxicosis of the exophthalmic type, had been totally incapacitated for three years. The basal metabolic rate was + 43 per cent, the pulse 120 per minute; there was marked nervousness and tremor, shortness of breath and great fatiguability.

This patient presented a pitiful appearance with his extreme nervousness and lack of concentration. His markedly prominent eyes, marked tremor and loss of weight had kept him from any gainful occupation for three years. He had received forty Roentgen ray treatments and courses of iodin in addition to the usual medical measures.

A total thyroidectomy was followed by slight postoperative reaction and an uneventful convalescence.

The patient's condition demanded thyroid extract, 1 gr. daily, three weeks following the operation. His basal metabolic rate at that time ranged from − 5 per cent to + 2 per cent and his pulse rate from 60 to 72 per minute.

At present, one year after the operation, this patient has gained 17 pounds in weight, feels perfectly well, has no symptoms and has been at work steadily since two months after his operation. His exophthalmos disappeared promptly. His basal metabolism is normal, his pulse 72 per minute. He requires 1 gr. of thyroid extract daily. He has been at work for nine months.

This patient is now calm, full of energy and averages 3 miles walking daily at his occupation of insurance broker.

CASE II.—W. L. B., aged fifty-four years, male, with thyrotoxicosis of the exophthalmic type, suffered total incapacity for four

years. The basal metabolic rate was +45 per cent, the pulse rate 120 per minute; the hands were moist and warm; tremor was present, also marked fatigue and shortness of breath.

This patient's vital capacity was but 50 per cent and shortly before operation on his attempting to work he became seriously ill and lost 40 pounds in weight.

As with the first case, this patient's condition was considered hopeless. He looked extremely ill and emaciated, had been unable to earn a living for over four years during which period he had been continuously under treatment. Definite cardiac decompensation was present with shortness of breath and swelling of the feet. He received a total of fifty Roentgen ray treatments and iodin in addition to the usual medical measures.

A total thyroidectomy was followed by no postoperative reaction and by a rapid and uneventful convalescence with disappearance of exophthalmos.

The basal metabolic rate fell to −16 per cent within a month after operation with symptoms of hypothyroidism. Thyroid extract was administered and the basal metabolic rate brought up to normal by thyroid feedings. He has no tremor.

Nine months later this patient is feeling well, his pulse is 72 per minute, his weight is 170 pounds—a gain of 40 pounds—and he has resumed his occupation of carpenter. He receives at present 2 to 3 gr. of thyroid extract a day. After a hard day's work at carpentering he walks for exercise, sleeps well, eats well and is happy.

CASE III.—A. H., aged twenty-eight years, female, married, had thyrotoxicosis of the exophthalmic type, with total incapacity for six years. The basal metabolic rate was +44 per cent, the pulse rate 116 per minute; there was marked nervousness and tremor, great fatiguability and loss of weight.

This patient's nervousness and exophthalmos were extreme as was her fatiguability. She had been unable to perform her household duties for six years. She received Roentgen ray treatment off and on for over a period of three years, iodin, and so forth.

A total thyroidectomy was followed by practically no reaction and an uneventful convalescence.

Following operation the patient's metabolic rate fell to −16 per cent after a month. The rate was brought up slowly by means of thyroid extract, the maximum being 3 gr. daily. Now the patient feels perfectly well, has gained 14 pounds, her pulse rate is 70 per minute, she feels strong and is able to do her housework, which she has been unable to do for years. Her exophthalmos has disappeared. She has been well since her operation ten months ago.

CASE IV.—G. C., aged forty-nine years, male, had thyrotoxicosis of the exophthalmic type, with nervousness, fatiguability and

weakness for the past year. This patient did not respond to rest and iodin and on account of his poor condition was subjected to ligation of both superior thyroid vessels. This did not appreciably alter his general condition or lower his basal metabolic rate. The latter remained above +80 per cent and his nervousness and motor activity were most marked. He was completely incapacitated from work and his motor nervousness was so great he was unable to recuperate by rest.

A practically total thyroidectomy was done, a portion of the lower left lobe, 1 by 1 cm. in size, being left. This operation was followed by no more, if as much, reaction than followed the ligation operation and patient's convalescence was uneventful and prompt.

The basal metabolic rate fell eleven days following the operation to +22 per cent. The pulse rate dropped to normal, the nervousness had disappeared as had the exophthalmos and the patient had resumed his occupation within two months. He is still at work and feels well. He has failed to report for three months for a basal metabolic reading but sends word he feels well and is hard at work as a contractor.

CASE V.—G. T., aged forty-five years, female, married, had thyrotoxicosis of the exophthalmic type, with total incapacity for three years. The basal metabolic rate was +60 per cent, the pulse rate 130 per minute; there were nervousness and tremor, fatiguability and loss of weight.

This patient was a thin, emaciated, nervous little woman showing marked fatiguability with despondency and discouragement. The usual measures, with the exception of iodin, were tried.

A total thyroidectomy was followed by a moderate reaction only, and an uneventful convalescence.

A month later her basal metabolic rate was −21 per cent and was readily brought up to normal by thyroid extract. The patient gained rapidly in weight, felt and looked like a young woman and was able to carry on rather strenuous housework. At present the pulse is between 68 and 72 per minute and she feels well. She is now, a year and a half after operation, receiving 1 gr. of thyroid daily and is well.

CASE VI.—F. S., aged twenty-seven years, male, had thyrotoxicosis of the exophthalmic type. This patient was incapacitated for three years and hospitalized for one year and received sixty Roentgen ray treatments and several courses of iodin during that period. His basal metabolic rate was +50 per cent, fatiguability was marked as was the patient's nervousness and tremor. He had lost a large amount of weight.

A practically total thyroidectomy was followed by no postoperative reaction and an uneventful rapid convalescence.

Within a month this patient was able to resume his studies at college. His basal metabolic rate was maintained at normal with periodic feedings of thyroid extract. When last heard from, a year after the operation, this patient was apparently perfectly well and extremely grateful.

CASE VII.—C. W., aged thirty-four years, female, married, had thyrotoxicosis of the exophthalmic type. This patient had been subjected to subtotal thyroidectomy eleven years previously. She did fairly well until two years ago but never lost her exophthalmos completely or her rapid pulse.

During the past two years the patient had a return of symptoms and before the present operation showed marked exophthalmos, a pulse rate of 120 to 130 per minute permanently, nervousness and great fatiguability with shortness of breath.

A practically complete thyroidectomy was followed by no postoperative reaction and a rapid uneventful convalescence. A piece of thyroid gland, approximately 1 by 1 cm., was left.

At present, one year after her operation, she looks and feels well, exercises vigorously, and her pulse rate is between 70 and 80 per minute. The exophthalmos has completely disappeared.

This patient passed through two experiences two months ago that apparently upset her not at all. She was operated on for pelvic trouble and later did vigorous work saving personal belongings when her house caught fire. Following these experiences the patient reported to see if she had injured herself. She was found to be, apparently, perfectly well.

CASE VIII.—H. W., aged forty-two years, female, single, with thyrotoxicosis of the exophthalmic type, showed markedly prominent eyes, extreme nervousness, tremor, loss of 40 pounds in weight and had been incapacitated practically for the past eight years and completely for the last two.

The lowest point attained by the basal metabolism after medical treatment, including Roentgen ray, rest and iodin, before coming to our clinic was + 30 per cent.

A total thyroidectomy was followed by an uneventful convalescence with no postoperative reaction.

One week after the operation the patient's basal metabolic rate was − 6 per cent. This was brought up to normal with 1 gr. of thyroid daily. At present, three months after the operation, she feels well, her pulse is 68 per minute, her nervousness has practically disappeared and she has gained 8 pounds in weight. The patient feels very grateful.

CASE IX.—E. W., aged nineteen years, female, single, had thyrotoxicosis of the exophthalmic type. This young woman had

been ill for two years. She showed a very marked nervous reaction, moderate exophthalmos, marked tremor with warm, moist palms and was incapacitated.

The basal metabolism was +42 per cent, the pulse varied from 110 to 130 per minute, and the condition resisted the usual medical measures, including Roentgen ray and rest.

A total thyroidectomy was followed by a moderate reaction as shown by a postoperative temperature of 101. Patient's convalescence was uninterrupted. Her basal metabolism was −5 per cent two weeks after the operation and she was given a ½ gr. of thyroid extract daily.

Six weeks only have elapsed since this patient was operated on but she already looks and acts like a different person. Her pulse is 74 per minute, she has gained weight, feels well and strong and her exophthalmos has nearly completely disappeared. She shows no tremor and her skin is of normal temperature.

CASE X.—S. M., aged twenty-six years, female, married, had thyrotoxicosis of the exophthalmic type. The patient was incapacitated from performing her household duties for about one year. She was nervous, had lost some weight and tired readily. On examination there was found some prominence of the eyes and stare, tremor and a pulse of 110 per minute.

A total thyroidectomy was done. This patient had been a trained nurse previous to her marriage and preferred surgery. Her convalescence was uneventful and the operation followed by no untoward reaction.

Shortly after the operation her basal metabolism was −14 per cent. She was given thyroid extract, 1 gr. daily, which restored her basal metabolism to normal.

At present, three months after the operation, the patient is well, feels cheerful, is able to work and has a pulse rate of 70 per minute.

In all of the cases the operations were performed with the patient under light nitrous oxid and oxygen anesthesia and both sides of the neck were blocked by injecting 0.5 per cent novocain previous to the incision.

Conclusions. 1. In selected cases at least, a total thyroidectomy is indicated. For all cases requiring operation a much larger amount of thyroid gland should be removed than is at present usually done as we believe the entire gland is diseased and normal should be substituted.

2. The postoperative reaction appears to be inversely proportionate to the amount of gland removed. This apparently applies likewise to the period of convalescence.

3. It is not difficult in cases of total thyroidectomy to maintain a proper thyroid balance with a thyroid preparation, if regulated from time to time by basal metabolic determinations. A number

of these patients are able to determine subjectively the amount of thyroid extract they require.

4. In seemingly hopeless cases of exophthalmic goiter the results of total thyroidectomy have been most gratifying. The patients after long periods of complete invalidism have resumed their usual occupations and enjoy good health. While we have confined total thyroidectomy for the most part to those patients who were seemingly hopeless and had been invalids for long periods of time, we feel that the procedure may be extended to embrace less severe cases. We feel this because: (1) The entire gland is diseased; (2) the amount to be removed is indeterminate and the subsequent action of the amounts of gland remaining is likewise indeterminate.

5. We realize the number of cases upon which this report is based is small. However, the uniformly good results appear to warrant this preliminary communication.

THE DIAGNOSTIC CRITERIA OF CHRONIC PARATHYROID INSUFFICIENCY WITH SPECIAL REFERENCE TO THE PHOSPHATE CONTENT OF THE BLOOD.

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Although the first definite description of the parathyroid glands was that of Sandstrom, a Swedish anatomist, in 1880, it has been pointed out by Walter Edmunds that there is in the Museum of the Royal College of Surgeons a specimen showing the parathyroid glands as well as the thyroid glands of the Indian rhinoceros. It was obtained in 1849, when the animal died in the Gardens of the Zoölogical Society of London. Sir Richard Owen reported the results of its dissection to the society in 1850. He described a small compact yellow glandular body attached to the thyroid at the point of emergence of the veins. This seems to have been the first anatomical description of the parathyroids as separate and individual organs.

After Sandstrom's description of the parathyroids, Weiss, in Billroth's Clinic in Vienna, reported the occurrence of tetany in some patients after removal of the thyroid for goiter, and named the conditions tetania strumipriva. In 1891 Gley showed that no tetany occurred in rabbits when the thyroid was removed. However, he misinterpreted his findings regarding the parathyroids as part of the hypertrophic mechanism of the thyroid. In 1896–1897 Vassale and Generali established definitely the distinction between the effects of removal of the thyroid as myxedema, or cachexia

strumipriva, and the effects of removal of the parathyroid as tetany. They therefore proved the existence of functional difference between the two organs as of structural difference. A number of subsequent observers and experimenters confirmed their observations.

The occurrence of tetany therefore became the criterion of parathyroid insufficiency. The peculiar spontaneous attacks of tonic spasm in the extremities causing them to assume characteristic attitudes became pathognomic. It was soon found that individuals with tetany of the extremities could also have spasms of the whole body musculature. Then it was found that these spontaneous attacks occurred in individuals who between attacks presented a specific hyperexcitability of the nervous system, and that tonic spasms could be provoked by various stimuli, preferably mechanical or electrical. This condition was described as latent tetany.

TABLE I.—COMPARISON OF ELECTRICAL IRRITABILITY OF ULNAR NERVE—CHVOSTEK REACTION, NORMAL BLOOD CALCIUM AND INCREASED BLOOD PHOSPHATE—IN CASES OF SUPPOSED PARATHYROID INSUFFICIENCY.

	Name.	K O C	K C C	A O C	A C C	Chvostek	Blood calcium.	Blood phosphate.
1	H. E. B.	3.9	1.2	1.1	2.8	xxx	12.4	3.0
2	F. S.	2.4	1.1	0.9	1.9	xx	11.8	5.1
3	M. F.	2.5	1.0	0.9	2.1	xx	9.6	5.0
4	E. K.	2.8	1.4	1.2	2.3	xx	10.4	5.1
5	F. C. M.	2.5	1.2	1.3	2.4	xxx	10.2	5.4
6	E. K.	4.0	1.9	2.5	3.8	x	10.2	4.5
7	J. K.	1.9	0.8	0.5	1.2	xxx	9.0	6.0
8	E. H.	3.1	1.1	1.0	2.3	xx	11.8	4.9
9	G. D. G.	4.5	1.8	2.9	4.0	x	10.1	4.2
10	M. L.	3.6	1.2	2.0	2.9	xx	10.2	4.8
11	E. H.	1.4	0.5	0.8	1.2	xxx	7.2	5.0
12	B. G.	4.2	2.2	2.6	3.2	xx	11.4	4.6
13	C. G.	1.8	0.9	0.5	1.1	xxx	11.2	5.6
14	L. F. K.	4.4	2.6	2.4	3.9	x	11.6	4.5
15	H. A.	4.0	2.2	2.0	3.5	xx	10.0	4.7
16	M. F. S.	1.8	0.7	0.9	1.2	xxx	10.0	5.7
17	F. P.	4.9	1.3	3.0	3.9	x	9.8	4.5
18	M. B. B.	2.0	0.7	1.2	1.6	xxx	9.6	5.5
19	F. D.	3.1	1.1	1.9	2.4	xx	8.3	5.0
20	E. C. D.	4.5	1.6	2.7	3.6	xx	9.3	4.6
	Average						10.2	4.89

The criteria for the diagnosis of parathyroid insufficiency therefore became: (1) Spontaneous attacks of tonic contractions in extremities ("accoucheur hand," carpopedal spasm); (2) of the facial muscles—trismus; (3) of the laryngeal muscles—laryngeal spasm; (4) mechanical hyperexcitability of the peripheral nerves—

the Trousseau, Chvostek and Poole phenomena, also called the arm and leg phenomena.

The Trousseau phenomenon and the Chvostek phenomenon were both described by clinicians in the period before their relations to the parathyroid glands was understood or guessed, the one in 1864 and the other in 1878.

TABLE II.—COMPARISON OF ELECTRICAL IRRITABILITY OF ULNAR NERVE—CHVOSTEK REACTION, NORMAL BLOOD CALCIUM AND NORMAL BLOOD PHOSPHATE—IN NONPARATHYROID CASES.

	Name.	K O C	K C C	A O C	A C C	Chvostek	Blood calcium.	Blood phosphate.
1	E. S.	6.2	2.4	3.6	4.4	0	11.6	3.0
2	B.	5.5	2.2	3.5	4.4	0	10.1	3.6
3	W. L.	5.0	1.8	3.0	4.1	0	9.8	3.6
4	R. H.	6.9	2.5	4.8	5.8	0	11.9	3.5
5	N.	6.0	2.1	5.1	5.2	0	11.3	2.6
6	E. S.	5.0	1.9	2.1	2.8	0	10.8	4.4
7	A. S.	6.5	2.8	3.9	4.8	0	11.2	4.1
8	F. O. S.	5.1	1.9	3.0	4.4	0	9.6	3.7
9	F. Mc.	4.9	2.0	2.9	4.1	0	10.1	4.1
10	J. S.	5.0	1.8	2.9	4.4	0	10.8	4.0
11	Th. T.	4.8	1.8	2.1	4.0	0	9.1	4.2
12	W. M. H.	5.8	2.2	2.2	3.8	0	11.9	4.2
13	J. J.	5.4	2.3	3.4	4.2	0	11.8	3.5
14	G. M.	5.0	2.5	3.2	4.0	0	11.8	3.6
15	H. D. K.	5.2	2.9	3.5	4.2	0	9.9	3.2
16	Ch. H.	5.5	2.5	3.6	4.4	0	10.0	3.8
17	A. H. N.	5.2	2.3	3.2	4.0	0	10.8	3.9
18	G. G.	6.0	2.8	2.9	3.9	0	10.1	4.2
19	M. J. G.	6.0	2.5	3.0	4.2	0	10.2	4.1
20	M. U.	5.1	2.2	3.0	4.4	0	10.6	3.9
21	E. A.	7.0	3.1	3.2	4.9	0	12.0	4.0
22	H. G.	5.4	2.6	3.0	4.1	0	10.9	4.1
23	W. S.	5.1	2.0	3.4	4.3	0	11.1	3.0
24	M. B.	5.3	1.9	3.1	4.0	0	10.1	3.9
25	B. G.	5.0	2.2	2.9	4.0	0	9.8	4.0
26	J. R.	6.9	3.2	4.1	5.2	0	12.0	3.9
27	H. G. S.	5.2	3.1	3.0	4.1	0	11.0	4.5
28	H. D.	6.5	2.6	3.8	4.9	0	12.0	3.8
29	K. S.	5.8	2.3	3.5	4.6	0	10.8	3.2
30	J. L. L.	5.0	2.2	2.9	4.0	0	10.2	4.1
31	C. C.	5.8	2.6	3.0	4.1	0	10.8	4.3
32	E. H. D.	5.0	2.1	2.8	3.9	0	9.7	4.3
33	A. D. L.	5.1	2.4	3.2	4.1	0	10.4	3.5
34	I. F.	5.5	1.8	2.9	3.6	0	9.8	4.1
35	L. B. D.	5.8	2.1	2.5	3.9	0	10.0	4.3
36	L. A.	5.0	2.2	2.2	3.5	0	9.8	4.3
37	M. W.	5.9	2.5	2.1	...	0	11.0	4.1
	Average						10.9	3.96

The Trousseau phenomenon is produced by the application of a ligature firmly about the upper arm. The pressure should be

sufficient to prevent perception of the pulse, and the palm should be stroked. It consists in the assumption of the obstetrical hand after three to five minutes.

The Chvostek phenomenon is the response to mechanical stimulation (tapping or pinching) of the facial nerve at its point of emergence from the parotid gland as the *pes anserinus*. There results a contraction of some or all of the muscles of the same side of the face; that is, there may be only a twitch of the angle of the mouth, or a twitch with a contraction of the nostril of the same side, or there may be these and a momentary twitch of the eye at the same time. These are classified as Chvostek X, XX or XXX.

The arm and leg phenomena were first described by Ferenczi in 1904 and by Poole in 1906. They consist in the production of carpopedal spasm upon hyperabduction of the arm and hyperflexion of the thigh with the knee extended.

The fifth criterion of parathyroid insufficiency is the measurement of the increased nerve irritability by a determination of the amount of galvanic stimulation necessary to act as a stimulus. Because first applied by Erb, this has become known as the Erb phenomenon. Von Pirquet standardized a procedure for its determination in 1907, and made a detailed study of the facts obtained. (One large electrode properly moistened and protected is placed upon the abdomen; the other stimulating small electrode is placed upon the nerve, ulnar, median or peroneal, to be stimulated. A quantitative measure of the degree of parathyroid insufficiency can thus be obtained.) For practical purposes a cathodal opening contraction, KOC, with a current of less than 5 ma. demonstrates increased galvanic excitability. When such KOC hyperexcitability cannot be elicited, the occurrence of a cathodal closing tetanus contraction, KCTe, with less than 5 ma. proves the existence of hyperirritability, although of a milder degree than that producing a KOC with less than 5 ma.

Clinically, certain manifestations may be looked for in chronic tetany or in tetanoid or hypoparathyroid conditions. The first is hypoplasia or defects of the enamel of the teeth. These manifest themselves as transverse grooves or furrows in the enamel, or as minute excavations in the enamel or as chalky looking spots in the enamel, which contrast with the appearance of the rest of the enamel. In children who have had a series of attacks of tetany these defects will appear as several parallel areas, each corresponding to a period of parathyroid insufficiency. Erdheim in his classic experiments on rats described a similar appearance of their teeth. Similar trophic disturbances of the nails may occur. A third trophic disturbance to look for is that known as perinuclear cataract. The dilated pupils reveal the perinuclear cataract when examined with a strong lens. Disturbances in growth of the hair may also be found quite frequently when looked for.

Chemically, two facts have been established concerning the blood and metabolism in parathyroid insufficiency. One is the loss of calcium from the tissues, a negative calcium balance being established while there is a definite lowering of the blood calcium. The other is the decrease in the phosphate content of the urine, accompanied by a retention of phosphate in the tissue in experimental tetany. Greenwald has recently reëmphasized this. In 1923 Salvesen, of Christiana, showed that in "latent tetany," that is, in parathyroidectomized animals kept alive by the administration of calcium salts, the calcium content of the blood is below normal and the inorganic phosphate is above normal. He made no observations on the electrical irritability of the nerves. In clinical latent tetany, however, or in individuals presenting other stigmata of chronic parathyroid insufficiency, I am aware of no studies in which the calcium content of the blood, the phosphate content and the electrical irritability of the nerves have been compared.

In studying individuals who presented themselves in office practice during the past year twenty patients were found who presented clinical stigmata of parathyroid insufficiency, increased electrical irritability and a positive Chvostek reaction. Chemically, however, they differed from typical examples in that the blood calcium fell within the average limit, or even above, of 9 to 11 mg. per 100 cc. But they, all except one, presented a blood phosphate definitely above the normal average, which lies between 3 and 4.5 mg. per 100 cc. A list follows showing the various data. The results have been compared with a series of individuals who showed no stigmata of parathyroid insufficiency. The conclusion may be drawn that at least in the milder forms of chronic parathyroid insufficiency, there need be no decrease in the calcium content of the blood, but there is always an increase in the inorganic phosphate of the blood.

Conclusions. These criteria therefore may be used in the diagnosis of chronic parathyroid insufficiency and in gauging the effect of treatment:

1. Dystrophies of the hair, nails, teeth and skin.
2. Mechanical hyperexcitability of the nerves: Trousseau and Chvostek phenomena.
3. Electrical hyperirritability of the peripheral nerves.
4. Diminished calcium content of the blood — negative calcium balance.
5. Decreased phosphate content of the urine — phosphate retention in tissues, increased phosphate content of the blood.

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PRIMARY CARCINOMA OF THE LUNG.

A Clinical and Pathologic Study from the Cook County Hospital, with a Report of 21 Necropsies and 3 Biopsies.

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Introduction. In reviewing the literature on primary carcinoma of the lung, one is struck by the fact that in spite of the marked increase in necropsy reports in the last few years, most writers still persist in calling the condition a rare one. It seems to us that Barron[1] struck the keynote when he wrote, "It has almost been a tradition that carcinoma of the lung is an extremely rare disease, of negligible clinical importance, and that its antemortem diagnosis is practically impossible." We wish to emphasize Barron's use of the word "tradition," and make an appeal for the elimination of the use of the word, and face the facts as they are, namely, that primary carcinoma of the lung is not a rare condition, and that it can be diagnosed antemortem.

Adler,[2] in 1912, stated that primary malignant neoplasms of the lung are among the rarest forms of disease, while Hampeln,[3] in 1919, wrote that since 1895 the idea of the rarity and inability to diagnose primary tumors of the lung has been gradually changed. Packard,[4] in 1917, wrote that medical literature has been extensively enriched by published reports on cancer of the lung. Whether this wealth of material is due to a greater efficiency in diagnosis or whether pulmonary malignancies are on the increase remains at the present a much mooted question.

Since 1917 the literature has contained an unusually large number of case reports, the majority of which are authentic, as they are accompanied by necropsy reports.

Our interest in this subject was aroused by having 3 cases of malignant tumors of the chest within a period of a few weeks in one medical ward at the Cook County Hospital. This report, therefore, includes 21 cases of primary carcinoma of the lung with necropsy reports and 3 cases with biopsies. This includes all necropsy reports from January, 1917, to September, 1924. We do not wish to review the historical side of this subject, but would refer the reader interested in it to Moise[5] and Ewing.[6]

Statistics. It is fortunate that many careful necropsy reports have been made on this subject. Wolf,[7] in 1895, reported 45 cases of primary cancer of the lung in 20,116 necropsies (0.223 per cent) performed at the Dresden Hospital from 1852 to 1894. Reinhardt,[8] in 1878, reported 5 cases among 8716 autopsies from the City Hospital of Dresden. Fuchs[9] reported 0.065 per cent in a series of 12,307 necropsies from the Pathological Institute of Munich, from 1854 to 1885. Krause cites Hesse as having found 99 cases in 63,088 necropsies.[10] Passler[11] reported 16 cases (0.183 per cent) of pulmonary carcinoma in 9246 postmortems in the Pathological Institute of Breslau. Lavrinovitch,[12] in 1915, reported 61 cases in 16,407 necropsies. Von Wiczkowski,[13] in 1913, reported 126 cases in 58,497 necropsies (0.21 per cent). Rolleston and Trevor,[14] between 1890 and 1902, reported 6 sarcomas and only 2 carcinomas in 3983 necropsies at the St. George's Hospital (0.05 per cent). Oerstrom[15] gave the percentage as 0.31 in 10,272 autopsies at the Charité Pathological Institute in Berlin from 1900 to 1907. Briese,[16] in a report from the Pathologic and Hygienic Institute of Chemnitz in 12,971 cases found 60 (0.46 per cent) of primary tumors of the lung. Cotton[17] reported 29 cases from the Cantonal Hospital in Geneva from 1900 to 1920. Weller,[18] in 1913, reported 0.3 per cent in 11,093 autopsies. Symmers[19] reported 5 cases from the Pathological Laboratory of the Bellevue Hospital from 1907 to 1919, while from July, 1919, to December, 1920, there were 8 cases. Knierim,[20] in 1909, reported 66 cases of bronchial carcinoma, 7 acanthomas and 2 alveolar tumors. Fishberg[21] reported 33 cases from the Montefiore Hospital from 1915 to 1920. Scott and Foreman[22] reported 3 cases in 302 autopsies. Barron[1] reported 13 cases in 4362 autopsies from the Department of Pathology of the University of Minnesota from 1899 to June, 1921 (0.29 per cent), and further states that from January, 1919, to June, 1921, there were 1003 necropsies, which included 9 cases of primary carcinoma of the lung (0.9 per cent). Moise[5] reported 5 cases in 375 consecutive autopsies (1.38 per cent). Playfair and Wakeley,[23] in a study of 3183 autopsies at the King's Hospital were able to find only 4 clearly established cases in the records from 1901 to 1923. This

is a surprisingly small number, and taken with Rolleston and Trevor's report makes one think that carcinoma of the lung in England is a very rare condition. Maclachlan,[24] in 1923, stated that during the past year he has seen four times as many cases as had been observed in the previous eleven years. He reports 5 cases in 375 autopsies.

From January, 1917, to September, 1924, 3659 autopsies were performed at the Cook County Hospital, and of this series there were 21 cases of primary carcinoma of the lung, a percentage of 0.57 of all necropsies.

Statistics by various authors indicate an incidence of 0.15 per cent or more of all autopsies, about 1 per cent of all carcinomas and 2 per cent of all deaths from pulmonary disease.

Etiology. In discussing the etiology of primary carcinoma of the lung one is just as much at a loss as with carcinoma elsewhere, although in recent years numerous authors, especially Moise and Barron, have suggested that the increase in carcinoma of the lung may be referable to postinfluenzal lesions. These writers refer to the work of Winternitz and his associates,[25] in 1920, in which they then suggested the probability of an increase in carcinoma of the lung on the basis of postinfluenzal lung changes. Moise[5] further states that even though no clinical history of influenzal infection is present, still it is quite conceivable to attribute the increase of carcinoma of the lung to postinfluenzal lesions. In only 1 case here reported was a history of influenza elicited.

Wohl[26] states that the recent wave of pulmonary infections, such as streptococcic bronchopneumonia and influenza, constitutes an important factor in the formation of pulmonary neoplasms. From the above, though the evidence is far from conclusive, it would seem more probable that acute inflammatory processes rather than chronic irritations play a strong role in enhancing the formation of neoplasms of the lung.

Most authors, including Ewing, have given tuberculosis as the chief etiologic factor; yet in only 1 of our cases was any evidence of pulmonary tuberculosis found. This to us seems worthy of mention, because of the fact that more than one-half of the autopsies at the Cook County Hospital are performed on colored patients, and the ravages of tuberculosis among the colored race are well known. The fact that only 2 of the 24 cases here reported occurred in colored patients appears to be significant. In the past the greatest emphasis has been placed on the association of tuberculosis with carcinoma, although it seems to us with very little ground, and now the recent increase in primary lung tumors would further tend to support Rokitansky's dictum. Carmen[10] stated that tuberculosis and carcinoma of the lung may exceptionally coëxist, although in 17 autopsies no tuberculosis was observed.

In 1878 Harting and Hesse described the Schneeberg carcinoma

of the lung, and stated that a lymphosarcoma of the bronchial lymph nodes or an endothelial sarcoma was responsible for 79 per cent of all the deaths among the miners of the Schneeberg district of Saxony. However, as autopsies are rare in this district, Arnstein suggested that it is possible that many cases were tuberculosis or pneumoconiosis.[27] That Arnstein's contentions were partly true may be surmised from a recent report by Saupe,[28] who stated that in the majority of the cases pneumoconiosis is found in the miners of Schneeberg, and sometimes there is an associated malignant tumor of the lung; while tuberculosis apparently plays a less important role. Saupe, therefore, believes that miners' disease in Schneeberg is caused partly by pneumoconiosis and partly by a true malignant tumor of the lung. Males are definitely more predisposed than females, the ratio being given as 3 to 1. In this series only 2 cases occurred in females. In Adler's series of 374 cases 113 occurred in individuals between fifty and sixty years of age. Seven in our series occurred between the above ages, while 6 occurred between sixty and seventy years. Our youngest patient was twenty-nine years of age, although primary tumors have been reported in children. The white race is definitely more predisposed than is the colored race. Heredity has not been shown to be of any importance.

TABLE I.—AGE INCIDENCE.

Years.	No. of cases.	Years.	No. of cases.
20 to 30	1	50 to 60	7
30 to 40	5	60 to 70	6
40 to 50	5		

Various authors have tried to associate the production of lung tumors with the after effects of gassing during the late war. Up to the present time no definite conclusions have been reached, although Haggard[29] states that chronic after-effects of gassing may result if the damage is severe enough to produce chronic inflammatory changes. These, for the most part, take the form of chronic bronchitis, pulmonary fibrosis and occasionally abscess formation.

Pathology. In considering the etiology of this condition from a pathologic viewpoint, it is natural that tuberculosis, a very frequent pulmonary condition, should be considered as important. Other pulmonary inflammations, such as bronchiectasis, influenza, chronic interstitial pneumonia and chronic bronchitis are also believed to be of etiologic significance. Ewing states that the chief etiologic factor is tuberculosis, and mentions the cellular overgrowth and alterations of bronchial and pulmonary epithelium found in the old sclerosis, atelectasis and reparative lesions of tuberculosis. Wolf[7] is stated to have found tuberculosis in 13 of his series of 31 cases of carcinoma of the lung, several of which showed active miliary dissemination, suggesting that the malignant process may light up

a latent tuberculosis. The association of pulmonary carcinoma with tuberculosis has been repeatedly cited in literature, although series have appeared in which the coexistence of the two was praccally absent. Rokitansky's old dictum that the presence of tuberculosis practically precludes carcinoma appears to be contrary to the generally accepted views concerning pulmonary carcinoma. The findings in the series of cases here reported would tend to sustain him, as in only 2 of the autopsies was any tuberculosis found, and only 1 of which was pulmonary in location.

Kaufmann[37] mentions the fact that pulmonary cancer develops in the walls of bronchiectatic cavities as well as those of tuberculous nature. Three of our cases were associated with bronchiectasis, but we agree with Barron,[1] that this is more often the result rather than the cause. Stenosis of the bronchi in consequence of the growth itself or of the inflammatory changes associated with it may easily give rise to bronchiectatic dilatation with cavitation.

Reports suggesting an increasing incidence of pulmonary carcinoma in the past three or four years have appeared repeatedly in the literature and our series seems to agree with these observations. The great influenza epidemic with the resultant acute inflammatory insults to the respiratory system has been held responsible for the decided increase in the number of cases reported. Winternitz, Wasson and McNamara,[25] in their study of the pathology of influenza, have pointed out the frequent destruction of the basement membrane of the epithelial structures, and they suggested in 1920 the probability of an increase of lung tumors on the basis of the epithelial overgrowth observed.

Adler,[2] in a study of 374 collected cases, found 188 of the cancers in the right lung and 157 in the left lung. Weller,[18] in an analysis of 89 cases, found the right and left sides affected with equal frequency. Barron[1] stated that the right lung is affected more often than the left, and the upper lobe more frequently than the lower. In Adler's series the most extensive change was in the upper lobe in 91 cases, in the hilar region in 90 and in the lower lobe in 75. Practically an entire lung was affected in 48 cases, and apical involvement was found in 16.

In our series the left side was affected in 12 cases, the right side in 5 and both sides in 3. The most extensive changes occurred in the upper lobe in 11 cases, the lower lobe in 5 and the whole lung was fairly uniformly affected in 4. In 17 the relation to the hilus was marked. Apical involvement was present in 5 cases, occurring as part of a disseminated invasion of the entire lobe or lung involved. In 8 instances the gross findings suggested an origin from a primary bronchus, 5 from a secondary bronchus and in 6 cases the origin was not grossly determinable. In one of the tumors the primary nodule appeared to be located in the lower part of the trachea. Ulceration of the bronchial mucosa at the site of the

growth occurred in 3 instances, while narrowing of the lumen of the bronchus involved was found in 7 cases, due either from pressure without or to actual plugging of the bronchus by the growth.

The gross appearances of these tumors present many variations, depending upon the stage at which the neoplasm is observed, and also upon the mode of growth. Adler makes note of the lack of uniformity of the gross appearances. The following forms have been described: (1) Infiltrating, (2) multiple nodular, (3) solitary nodular, (4) miliary and (5) mixed.

Kaufmann[37] describes an infiltrating form resembling a caseous pneumonic involvement of an entire lobe. Aschoff[38] describes similar grayish or yellowish masses with poorly defined limits and of very uncertain origin. Moise[5] notes that the infiltrating type is the usual one seen in advanced stages. McMahon and Carmen[39] describe a form which arises from a large bronchus with penetration of the wall and invasion of the lung tissues along the bronchi, bronchioles, alveolar walls and air spaces. Massive involvement of a single lobe or lung may occur by way of the lymphatics, blood-vessels, direct extension, gravity and aspiration. Adler mentions another type of infiltrating tumor starting from a smaller bronchus or bronchiole affecting only a portion of one lobe with a very dense growth.

Gross characteristics conforming with the above description were encountered in 11 of our cases. Of these 1 was considered alveolar and 10 bronchiogenic in origin. The growth was limited to a lobe in 8 instances, while in 3 all the lobes of a lung were involved. In all of these the tumor had evidently arisen in the hilus and extension was occurring peripherally to involve the parenchyma of the lung. No apical involvement was noted in any of the above cases, although invasive characteristics were more or less pronounced in all of them. Degenerative changes were noted in all but 3.

A solitary nodule, occurring very rarely, is described deeply buried in the tissues of a lobe. This may be surrounded by a few minute miliary nodules. This type produces slight symptoms or none, and is said to occur very rarely. Two such tumors were found in our collection. In 1 of these there was a small circumscribed tumor mass about 3 cm. in diameter buried deeply in the substance of the right upper lobe. The other existed as a solitary nodule in the hilum of the left lower lobe. Neither of these were invasive in character, nor did they show degenerative changes. Following histologic study one was considered bronchiogenic in origin and the other a questionable bronchiogenic type.

A multiple nodular type, involvement at first being limited to one portion of the lung, is described by Adler. The nodules may be very numerous, with marked variation in size and with sharply defined boundaries. There may be a rather large circumscribed tumor mass in the center of the lobe, surrounded by nodular foci,

which may eventually involve other lobes. This type occurred twice in our series. In the first there were many nodules distributed diffusely throughout both lungs, while in the second there was widespread involvement of only the right lung. Narrowing of the lumina of the adjacent bronchi occurred in both cases, while degenerative changes were noted in the nodules of one.

A miliary form is described, resembling tuberculosis, with symmetrical and diffuse involvement throughout both lungs, the tumor being slightly larger than tubercles. The nodules are more or less translucent white in color. Involvement occurs along the course of the lymphatic channels, indicating an early lymphatic invasion of the lung. This type of growth was met with only once in our series. This, however, did not conform with the accepted picture, as only the left lung was involved. The nodules were very small, some being 1 to 2 mm. in diameter. The distribution throughout the affected lung was very diffuse; the periphery, central portions, apex and the base were equally involved.

The mixed type presents a combination of infiltrative and miliary or nodular forms in the same case. In addition to an infiltrating mass in one or more lobes, the remainder of the lung is diffusely studded with nodules varying in size and number. Four of our cases corresponded grossly to the above description.

Histologically pulmonary carcinoma shows a rather varied picture. The following classification as to cell type has been used: (1) Cylindrical-cell carcinoma, (2) squamous-cell carcinoma, and (3) mixed-cell type.

Cylindrical-cell carcinoma has been subdivided into numerous groups on the basis of histologic structure. Adenocarcinoma is reputed to be the most common, the structure presenting a glandular appearance. Carcinoma simplex, composed largely of solid masses of tumor cells is supposed to arise from bronchial epithelium or from mucous glands. A scirrhous type occurs characterized by a slow growth and enormous amounts of connective-tissue proliferation with relatively few tumor cells. Alveolar carcinoma is characterized by solid masses of pleomorphic cells occupying spaces resembling lung alveoli. A medullary carcinoma has been described, resembling sarcoma; which is composed of compact, small pleomorphic cells having little cytoplasm. Colloid or gelatinous carcinoma derives its name from the rich colloid content.

Squamous-cell carcinoma is believed to occur as a result of metaplasia of cuboidal epithelial cells. Another theory accounts for its occurrence on the basis of embryonic displacement of islands of squamous cells. Most of these tumors are believed to originate in the scars and walls of tuberculous cavities.

A mixed type has been encountered in which there are several of the above types of cells and structures in the different portions of the same growth.

In 55 cases reviewed by Weller,[18] 45 were alveolar, acinar or adenomatous, 5 were medullary, 3 scirrhous and 2 simplex. We are unable to review the histologic structures of this series of tumors, because detailed microscopic records are not available in many of the cases.

Attempts to establish the histogenesis of cancer of the lung have naturally been directed at the three types of epithelial cells which occur in the pulmonary system. However, it is admitted that it is impossible to determine the histogenesis of the majority of the tumors, because of the uncertainty associated with the morphology of the cells. It is essential that the cases be studied during the early stages of the disease. Other difficulties result from the modification of the tumor cells as a result of inflammatory processes to which lung tissue is susceptible. In addition the secretory cells of the mucous glands, the pavement cells of the alveoli and the bronchial epithelium are closely related morphologically, the first two being merely modified columnar cells which line the bronchi.

The ordinary criteria by which many tumors have been classified histogenetically are inaccurate, since some of the authors have attributed alveolar origin to tumors composed of squamous cells, merely because they happen to resemble the flat cells lining the alveoli. Since bronchial epithelial cells, as well as mucous gland epithelium, may secrete mucus, it is inaccurate to trace the origin of tumors to the latter, simply because the neoplasm presents an abundant mucoid secretion.

Under ordinary circumstances, therefore, it is obviously impossible to definitely classify a given pulmonary carcinoma according to its histogenesis, and yet this is the most prevalent method of classification. Ewing[6] discusses these tumors under headings of those arising from: (*a*) Bronchial epithelium, (*b*) alveolar epithelium and (*c*) bronchial mucous glands. He also states that to a considerable extent these types are distinguished by gross anatomic features and by certain clinical ones. He modifies this by saying that it is difficult to separate all advanced cases, especially the more malignant types; for the specific features belong chiefly to the earlier stages. In discussing the histogenesis, he states that there are comparatively few opportunities to trace the origin of this type of neoplasm. He regards conclusions as to histogenesis reasonably certain upon the evidence of histologic structure, gross anatomy and clinical history.

We believe that a histogenetic classification of these tumors is not acceptable under ordinary circumstances because the histologic studies are confusing and inaccurate, the gross anatomic findings are not characteristic and, finally, the clinical history of little or no value. Our series of cases were examined by competent and well-trained pathologists, who classified each tumor under one of the above three headings. Sixteen were considered to be of bron-

chogenic origin, 2 alveolar, 1 of mucous gland origin and 2 questionable. In reading the gross reports it is evident that most of these tumors were too far advanced to allow gross anatomic appearances to be of value. It is evident that classifying these neoplasms as arising from one or another type of epithelium admits great probability of error. It may be truthfully stated that many of the tumors reported in the literature as bronchiogenic, alveolar, and so forth, are subject to the same inaccuracy. In submitting our version of the histogenesis of our tumors we desire to demonstrate only the usual conclusions reached, and do not present these as accurate studies in histogenesis.

The consensus of opinion is that the majority of these tumors arise from the bronchial epithelium, and that only a few arise from the parenchymal or alveolar epithelium. Adler[2] states that a primary carcinoma of the lung is a bronchial carcinoma. Kaufmann,[37] on the other hand, believes that the origin is most frequently from the mucous glands.

Ewing describes carcinoma of the bronchial lining epithelium as producing extensive changes in the bronchial mucosa, advancing along the walls of the bronchi, septa and pleura, but seldom producing a diffuse tumor of the lung. The process usually begins at or below the bifurcation and extends toward the trachea above and the smaller bronchi below. The bronchi may be filled with papillary projections over a wide area invading the parenchyma and producing a thickening of the walls. Ewing quotes Chiari, Tillman and Peck in stating that the presence of very high cylindrical cells and their persistence in metastases indicate an origin from the bronchial mucosa.

Tumors arising from the mucous glands have been described as having quite characteristic gross and microscopic features. Limitation of the growth chiefly to the walls and submucosa of the bronchi, freedom from ulceration of the mucosa, narrowing rather than dilatation of the bronchi and an adenocarcinomatous or alveolar carcinomatous structure with cell groups resembling mucous glands, are features considered more or less characteristic of this type. The secretion of mucus, although occurring also in tumors arising from bronchial mucous lining, is a prominent feature of this type, and is strongly suggestive of mucous gland origin. However, the age of the growth, the rapidity of the same and secondary changes may result in marked variations from the typical structure and gross findings.

Ewing describes diffuse and nodular types of carcinoma arising from pulmonary alveoli. In the diffuse form an entire lobe or lung is uniformly consolidated, the lesion resembling the gray hepatization of croupous pneumonia or an organizing pneumonia. The structure of these tumors shows a filling of alveoli with cuboidal, cylindrical or flat cells, the vesicle walls being either preserved or

TABLE II.—VARIOUS METASTASES.

| Case. | Lymph metastases. | | | | | | | | | | Regional metastases. | | | Organic metastases. | | | | | | | | | |

TABLE III. — ASSOCIATED LESIONS.

Case.	Type.		Lungs.				Bronchi.		Pleura.						Pulmonary osteoarthropathy.	Tuberculosis.		Pathologic Fracture.	Mediastinitis.	Compression of sup. vena cava.
	Bronchogenic.	Alveolar.	Submucous.	Compression atelectasis.	Pneumonia.	Hyperemia, hypostatic or passive.	Abscess.	Chronic indurative.	Suppurative.	With cavitation and abscess.	Without cavitation.	Obliterative.	Focal.	Fibrinous.	Serosanguineofibrinous.	Hemothorax.	Hydrothorax.	Empyema.					

obliterated by tumor growth or inflammatory changes. The nodular form presents in one or both lungs multiple tumor foci varying in size and showing necrotic areas. The structure of this type shows groups of slightly dilated air vesicles filled with papillary projections of cylindrical cells.

Authentic cases of alveolar origin are very rare. Passler,[11] in discussing the alveolar origin of tumors, stated that 47 of the 54 reported alveolar tumors or 8 per cent were apparently bronchial in origin.

The metastases of pulmonary carcinoma are widespread, only a few cases being reported without secondary growths. Due to the great vascularity of the organ and the abundant lymphatic channels, widespread dissemination by way of the blood stream and regional extension by way of the lymphatics frequently occurs. Of the 374 cases reported by Adler there was invasion of the bronchial nodes in 117; mediastinal in 45; tracheal, 26; cervical, 23; retroperitoneal, 23. The liver was invaded in 103 cases; pleura, 52; pericardium, 39; heart, 30; kidneys, 58; adrenals, 38; spleen, 18; brain, 53; bones, 47. Metastases were absent in 33 cases.

All of our cases showed metastases to the regional lymph nodes and distant organs. In only 3 of the 21 autopsies were metastases limited to the regional lymph nodes, the others showing involvement of distant organs as well.

The following groups of glands were involved: Tracheobronchial and mediastinal, 18; periaortic, 5; cervical, 6; abdominal, 3; iliac, 1; femoral, 1; axillary, 1; perigastric, 2; peripancreatic, 2; peribiliary, 2; periesophageal, 1. The following regional metastases were found: Lungs, 13; pleura, 8; pericardium, 7; mediastinal and cervical tissue, 5; trachea, 1. Metastatic deposits were found in the following organs: Liver, 12; adrenals, 5; kidneys, 8; bones, 8; brain, 5; heart, 1; appendix, 2; skin, 3; spleen, 2; omentum, 1; mesentery, 2; pancreas, 4; thyroid, 1; tonsil, 1; tongue, 1; ileum, 2; dura mater, 1; peritoneum, 2. Metastases occurred in the following bones: Ribs, 5; calvarium, 2; vertebra, 1; zygoma, 1; ilium, 2; neck of the femur, 1; occipital bones, 1; sphenoid, 1. Three instances of pathologic fracture were encountered.

Consideration of the associated pathology is important because these secondary complications frequently alter the clinical and pathologic picture. Adler found pleural fluid of varying amounts in 46 of 374 cases. Cavities small or large, single or multiple, in the carcinomatous tissue were found in 60 cases. Bronchiectasis was found in 28 instances. Only 19 were associated with tuberculosis. Atelectasis from bronchial obstruction or compression and pneumonias of various types were mentioned in a few cases.

Dana and McIntosh[40] found 37 instances in the literature of obstruction of the superior vena cava by carcinoma of the lung. In 14 of these cases the carcinoma was primary in a bronchus. In

only 6 cases was the diagnosis verified by autopsy. Two of our series of cases showed superior vena cava obstruction at postmortem examination, both of which occurred in tumors arising from the right side. One of these cases presented edema of the neck, thorax and upper extremities and also varices of the veins of the neck and scapular region. In 1 case a tumor thrombus was found in the left pulmonary vein.

Compression atelectasis of the lungs occurred in 7 of the necropsies and pneumonias of various types were noted in 9. Pulmonary abscess was recorded in 5 of the autopsies, and hypostatic and passive hyperemia in a similar number. Bronchiectasis with cavition was seen in 3 cases, with 2 of which pulmonary osteoarthropathy was noted. Chronic bronchitis (indurative, 1; suppurative, 3) was encountered in 4 cases. Pleuritis occurred in a relatively large number of cases, the following forms being found: Chronic obliterative, 8; focal fibrous, 4; acute fibrinous, 3; acute serosanguineofibrinous, 3; suppurative, 1. Hemothorax was seen in only 3 cases, and hydrothorax in 2. Contrary to the generally accepted views, only 2 cases of healed tuberculosis were recorded, 1 pulmonary and 1 glandular. Emaciation was very prominent in 6 cases.

Symptoms. There are no pathognomonic symptoms of carcinoma of the lung; yet, the disease presents, as a rule, symptoms which should lead one to suspect its presence. Symptoms may vary greatly, in some cases being only pulmonary in character, in others consisting only of metastatic phenomena, while in others symptoms of a localized tumor are found, in others symptoms only of a pleural effusion are found and, finally, cases are seen in which no clinical phenomena are present.

In the series of cases here reported the most common symptoms in order of frequency were weakness, cough, expectoration, pain in the chest and dyspnea. Other symptoms noted were loss of weight, fever, night sweats and hemoptysis. Pain in the chest, which is frequently an early symptom, is usually of insidious onset, unilateral and of a dull, aching nature, although at times it may be sharp and stabbing. At times the pain is referred down the arm on the same side or is localized in one of the shoulder joints, possibly from referred pleural irritation. Fishberg and Steinbach lay great stress on the presence of pain in the chest as a great help in differentiating carcinoma from tuberculosis.

The cough has nothing characteristic. It usually is accompanied with some expectoration, which consists of yellowish mucus. In regard to the black currant jelly sputum upon which so much stress has been placed, nothing definite can be said, except that it is absent in more cases than it is present. In only 1 case in this series was a prune juice sputum observed.

Dyspnea is a symptom which may be present to only a slight

extent or may become orthopneic in character, or at times may resemble the dyspnea observed in bronchial asthma.

Weakness was a prominent symptom in all of the cases in this series, and was complained of by all as a feeling of excessive tiredness and gradual loss of strength.

Hemoptysis was noted only in 5 cases, although Fishberg states that in one-half of his cases hemoptysis was an early symptom.

A symptom concerning which there has been a great deal of discussion is fever. Weller emphasized the diagnostic importance of the absence of fever and night sweats, while on the other hand Hamman[30] stated that tumors of the lung are nearly always accompanied by fever, more commonly high and continuous. In regard to this point, we wish to state that it was the continuous absence of fever in 3 cases which led us to suspect carcinoma of the lung and which helped in finally diagnosing this condition. In 2 cases of these series the temperature was high and continuous, in 1 reaching 103° F., while in another case the temperature was pyemic in character. In most of the cases only a slight and occasional rise in temperature was noted. The presence or absence of fever will, of course, depend a great deal upon whether there is secondary infection in the tumor or not. From the above it would seem that Weller's statement in regard to fever was more nearly correct.

Loss of weight was present in all of the cases, and in most instances was quite marked, varying from 15 to 75 pounds, in a period of two to three months. As far as the pulse rate is concerned, nothing definite was noted, some cases showing a rapid pulse rate, while most of the cases showed no increase.

The physical findings which are most prominent are an area of marked circumscribed dulness with diminished or absent breath sounds, with diminished vocal and tactile fremitus and no rales. In cases in which the growth does not completely compress a bronchus one may get bronchial breath sounds, which have been called "cornage." This was first described by Behier. In regard to pleural effusion, Hamman[30] states that the pleura is commonly involved in tumor of the lung, and that pleural effusion is one of the chief symptoms. Bridges and Moser[31] state that all types of lung cancer produce pleural involvement, and this generally early in the course of the disease. In only 8 of this series were there pleural metastases with pleural effusion. This would not bear out the above statements in regard to early pleural involvement. As most writers have stated, the fluid accompanying pulmonary neoplasms accumulates very rapidly and has a tendency to completely fill the chest. The character of the fluid may vary from serous to bloody or a purulent type. The presence of a bloody pleural exudate suggests to many the possibility of malignancy, although Horder[32] states that the commonest cause of blood-stained pleural effusion is not malignant disease, but tuberculosis. Cell counts

on the pleural fluid showed a preponderance of lymphocytes. Bridges and Moser[31] report 2 cases and Rusk and Randolph[33] 1 case in which carcinoma cells were found in the aspirated pleural fluid. In view of this finding, it would seem advisable to look for tumor particles more carefully in suspected cases.

The great majority of cases in this series showed a leukocytosis in the blood stream, varying from 9000 to 20,000. Packard,[4] in his 7 cases, reported a leukocytosis varying from 10,000 to 20,000.

In regard to blood pressure a point may be brought out of some value. We all know the tendency to hypotension in cases of tuberculosis. In this series of cases in only 1 was a blood pressure below 100, that is, systolic, recorded. The finding, therefore, of an increased or normal blood pressure in an individual in whom one is trying to differentiate tuberculosis from a lung tumor, may be a thread, though slight we realize, of help in substantiating the diagnosis of a lung tumor.

The course of carcinoma of the lung may vary from weeks to years. Cases of four years' duration have been reported by Adler and also by Pinchin.[34] Eight months was the longest duration of symptoms in this series.

Diagnosis. One of the prime requisites in diagnosing any disease entity is an appreciation, which should be constant, of the possible presence of that disease. If this were kept in mind we are quite certain that diagnoses of carcinoma of the lung would be made much more frequently than they are. Moise[5] states that lung tumors are only rarely diagnosed antemortem, and yet, at the Cook County Hospital, where the majority of diagnoses are made by the internes on the staff, 8 cases of this series of 24 (33.3 per cent) were correctly diagnosed antemortem. Fishberg and Steinbach,[21] in their series of cases were able to obtain a much more enviable record of antemortem diagnoses.

Fishberg and Steinbach[21] discuss the diagnosis of lung tumors in such a masterly fashion that we take it upon ourselves to quote freely from their article. They state that nearly all patients with malignant growths of the chest cough and expectorate sputum. It is important to think of a pulmonary neoplasm when a patient in the cancer age, showing no symptoms of cardiac, renal or arterial disease, begins to cough and is short winded. In patients who have passed middle age pain in the chest with or without pleural effusion is suggestive.

In a patient, therefore, who is of middle age or past, and who has unilateral findings of an area of dulness or flatness, associated with decreased or absent breath sounds or amphoric breath sounds; if in addition that patient has pain in the chest, with or without dyspnea, then one should strongly suspect a lung tumor. Rales appear rather late in neoplastic growths.

TABLE IV.—SYMPTOMS.

Case.	Sex.	Race.	Age.	Duration symptoms.	Pain in chest.	Cough.	Expectoration	Hemoptysis.	Cyanosis.	Dyspnea.	Weakness.	Loss of weight.	Night sweats.	Rise in temperature.
1	M.	W.	29	?	+	+	+	○	○	○	+	+	+	+
2	M.	W.	64	4 months	○	○	○	○	○	○	+	+	○	○
3	M.	W.	45	6 months	+	+	○	○	+	+	+	+	○	+
4	M.	W.	45	2 months	+	+	+	○	○	○	+	+	○	○
5	M.	W.	65	3 months	○	○	○	○	○	○	+	+	○	○
6	M.	W.	52	4 months	+	+	+	+	○	○	+	+	○	○
7	F.	W.	69	4 months	○	+	○	○	○	+	○	+	○	○
8	M.	W.	65	2 months	○	+	+	○	○	○	+	+	○	○
9	M.	W.	42	4 months	+	○	○	○	○	○	+	+	+	○
10	M.	W.	39	2 months	+	+	+	○	○	○	+	+	○	○
11	M.	W.	57	1½ months	○	+	○	○	+	+	+	+	○	○
12	M.	W.	38	3 months	○	○	○	○	○	+	○	+	○	○
13	F.	Col.	70	5 weeks	○	+	+	○	○	+	+	+	○	○
14	M.	W.	50	1 month	+	+	+	○	○	○	+	+	○	○
15	M.	W.	57	5 weeks	+	+	○	○	+	+	+	+	○	○
16	M.	W.	60	?	○	+	+	+	○	○	○	+	○	○
17	M.	Col.	50	4 months	+	+	○	+	○	+	+	+	○	○
18	M.	W.	33	1½ months	+	+	+	○	+	+	+	+	+	+
19	M.	W.	44	2 months	+	+	+	+	○	+	+	+	○	+
20	M.	W.	31	2½ months	+	+	+	○	○	○	○	+	+	+
21	M.	W.	36	1½ months	○	+	+	○	○	○	+	+	○	+
22	M.	W.	45	8 months	○	+	+	○	○	○	+	+	○	+
23	M.	W.	55	4 months	○	+	○	○	○	○	+	+	○	+
24	M.	W.	55	2 months	+	+	+	+	○	○	○	+	+	+

Of late many men have been advocating bronchoscopy for the early diagnosis and treatment of lung tumors. Jackson and his associates[35] state that the bronchoscope has brought to the aid of the surgeon an absolute certainty of diagnosis not otherwise possible and, what is even more important, this absolutely certain diagnosis can be usually made at such an early stage that there is a chance to save the patient by lobectomy. They further state that deformity and fixity of the bronchi involved in the infiltrative process are very characteristic, and in the endobronchial cases either a mass, nodule, fungation or ulcer is present.

As further aids to the diagnosis one should remember biopsy examination of lymph nodes whenever they are accessible or examination of tumor particles removed by way of the bronchoscope. The sputum should be examined for tumor fragments or carcinoma cells, although this has proven very difficult and of little value. Examination of pleural exudates for carcinoma cells should also be made.

Many writers have stated that roentgenology offers little help in the diagnosis of lung neoplasms. On the other hand, about an equal number have stated that the Roentgen ray is of great help in making the diagnosis. Carmen[10] states that because of complicating factors, such as pleural effusion, interference with pulmonary circulation, atelectasis, bronchiectasis, tuberculosis and other pneumonic processes, there can be no constant Roentgen ray picture for carcinoma of the lung. However, he propounded Roentgen ray findings which should lead one to suspect carcinoma. In 3 of our cases the Roentgen ray made the diagnosis.

In the differential diagnosis one must first exclude tuberculosis. In this connection the persistent absence of tubercle bacilli in the sputum with marked symptoms and signs of pulmonary pathology should always arouse one's suspicion. Fishberg and Steinbach emphasize the importance of dyspnea and pain in the chest as hardly ever being seen in early phthisis. Conditions sometimes come up which are not pulmonary in nature, but which must be differentiated because of metastatic phenomena. Such conditions as tuberculous meningitis, brain tumor, chronic arthritis, gastrointestinal diseases and other diverse conditions occasionally must be considered. Pulmonary conditions to be differentiated include interlobar effusions, encysted empyemas, pneumoconiosis, bronchiectasis, lobar pneumonia and various mediastinal new growths.

Prognosis. As yet no definite treatment has been offered for carcinoma of the lung and, therefore, the prognosis remains quite hopeless. However, with the advent of bronchoscopy it is possible that some cases may receive early diagnosis and possible removal of the tumor.

Treatment. Measures relating to the treatment of this condition have as yet been unsuccessful. Surgical intervention is very

difficult, because the large majority of tumors start near the root of the lung, metastases occur rather early and, in addition, one is confronted with the presence of the large pulmonary vessels and the important mediastinal contents. Lenhartz, in attempting operative interference, was successful in 1 case out of 5, this case surviving eighteen months. Morriston Davies[23] reported a successful case of resection of a lobe of the lung for carcinoma of the lung. The recent report of Jackson and his associates[35] will surely stimulate the medical profession in having trained bronchoscopists make examinations of cases somewhat indefinite in diagnosis, and in this way help in the early recognition of lung neoplasms, with the resultant earlier institution of treatment.

Orton[36] reported a case of a pedunculated growth resembling a polyp just below the middle lobe bronchus on the right side. The growth was removed through the bronchoscope and proved to be a carcinoma of the papillary type. Green[36] also reported a case of a tumor in the left primary bronchus which was removed through the bronchoscope. The removal of tumors through the bronchoscope opens up a field, the results of which will be waited for in the future.

Deep Roentgen ray and radium treatment have been tried with little results.

Case Reports. CASE I.—C. C., a white male, aged twenty-nine years, was admitted to the hospital, October 3, 1921, complaining of cough, expectoration, pain in the chest and neck, night sweats and loss of weight. On physical examination the lungs showed dulness throughou t,particularly at the apices posteriorly. The breath sounds were prolonged, especially the expiratory phase. Many rales were heard throughout both lungs, more marked at the apices. During the patient's stay in the hospital he continued to grow weaker and began to complain of rigidity of the neck. There was a daily temperature fluctuating between 98.6° and 103° F. About a week before death the patient became delirious. The red blood count was 4,200,000; white blood count, 13,600, hemoglobin, 70 per cent. The urine was negative. Sputum was repeatedly negative for tubercle bacilli. Roentgen ray of the chest showed apical and peripheral shadows suggesting tuberculous involvement. A shadow suggesting encysted fluid was seen at the right cardiodiaphragmatic angle.

Necropsy. (November 15, 1921, by Dr. Moody.) The right lung does does not collapse and is everywhere solid. It weighs 1220 gm. On the surface there are nodules as large as 2.5 cm. in diameter, which are white and somewhat umbilicated, having a consistency of tumor tissue. Surfaces made by cutting the lower lobe showed one large tumor mass about 10 cm. in diameter composed of firm, white tissue. Throughout the remaining portions are many nodules which replace most of the lung tissue. The upper lobe is similarly studded. The left lung weighs 680 gm. and contains numerous tumor nodules.

Anatomic diagnosis: Primary carcinoma of the right lower lobe of the lung; metastatic carcinoma of the upper lobe of the right lung, both lobes of the left lung, brain, kidneys, eighth rib, liver, pancreas and spleen; metastatic carcinoma of the omentum, mesentery of the small bowel, adrenals, tracheobronchial and cervical lymph nodes; tumor infiltration of

the calvarium with perforation; mucopurulent tracheobronchitis, left focal fibrous pleuritis.

CASE II.—A. M., a white male, aged sixty-four years, was admitted to the hospital, October 16, 1923, complaining of loss of weight and asthenia. Physical examination revealed in the neck a large mass of discrete freely movable lymph glands in both supraclavicular fossæ. The lungs were negative. Abdomen showed fulness and tympany with slight tenderness and resistance in the epigastrium. There were no palpable masses or organs. Because of the suspicion of neoplastic disease in the gastro-intestinal tract an exploratory laparotomy was performed. This failed to reveal any lesions in the abdomen. The patient went steadily downhill, and died, October 27, of a terminal bronchopneumonia. The red blood count was 4,640,000; white blood count, 9700; hemoglobin, 80 per cent. The blood Wassermann was negative.

Necropsy. (Dr. Singer.) The right lung is distended and covered with fibrous tags. The parietal pleura is adherent over most of the upper lobe. Near the hilum of the right lung is a mass of tumor tissue about 3 cm. in diameter. This is firmly attached to the surrounding structures, and on section it is white and a milky juice can be expressed from it. The left lung was normal, except for a congestion of the lower lobe.

Anatomic diagnosis: Primary carcinoma of the right lung; tumor metastases to the tracheobronchial, cervical and subpleural nodes on the right side; obstructive volvulus of the sigmoid; recently amputated appendix; localized suppurative perityphilitis; bronchopneumonic foci of the right lower pulmonary lobe; submucous fibroma of the stomach; left focal fibrous pleuritis; obliterative right fibrous pleuritis.

CASE III.—F. B., a white male, aged forty-five years, was admitted to the hospital, October 13, 1920, with a complaint of pain in the chest and right scapular region, dyspnea and cough of about six months' duration. The onset of his illness was gradual with general malaise, cough and pain in the chest. Four weeks prior to entrance into the hospital he quit work because of severe and persistent pain in his chest, particularly over the sternal region. In the past five months he had lost 15 pounds. Examination of the patient was essentially negative, but in view of the slight afternoon rise in temperature with a rather rapid pulse and a history of cough and pain in the chest a diagnosis of pulmonary tuberculosis was made. On October 14 a Roentgen ray of the chest showed an upper right lobe fibrosis with evidence of a cavity in its center. This was interpreted as being either a collection of small bronchiectatic dilatations or a cavity *per se*. Repeated examinations of the sputum with and without antiformin failed to reveal any tubercle bacilli. The blood Wassermann test was negative. Nothing further developed until December 2, when the patient became cyanotic, dyspneic and had marked prominence of the veins on the right side of his neck and right arm. Physical findings were those of a solid tumor in the right apex causing pressure on the superior vena cava. Roentgen ray examination at this time showed a very diffuse shadow density in the right upper pulmonary area. This appeared somewhat like a tumor, although a pneumonic phthisis was not ruled out. The left pulmonary area showed a very distinct increase of density which had the appearance of a very florid stage of fibroid phthisis. No further developments were noted until May 1, 1921, when the superficial veins of the chest, face, scalp, arms and abdomen were found distended. Flatness was elicited over the entire right lung with exaggerated tactile fremitus and tubular breathing. Over the left lung decreased resonance throughout with bronchovesicular breathing and a few rales were heard. The patient died May 5.

Necropsy. (Dr. Stangl.) In the upper region of the mediastinum there is a hard tumor mass about 15 by 10 by 12 cm., which encloses the trachea, bronchi and large vessels of the neck. When the trachea and bronchi are opened there is found in the entire lining of the right bronchus numerous white nodules and ulcerating white cancerous areas. The lumen of this bronchus admits with difficulty the tip of the little finger. The left bronchus is free and its lining is unchanged. The right lung is firm and crepitation is absent everywhere. The pleural covering is markedly thickened and about 3 mm. in some areas. The cut surface shows a black moderately wet parenchyma in which no areas of consolidation or tubercle formation are seen. The right bronchus for a distance of 10 cm. distal to the bifurcation is surrounded by a layer of cancerous tissue, 3 mm. in thickness. The left lung is also partially collapsed, dark purple to black in color, and on palpation crepitation is markedly diminished, but no nodules or tubercles are felt. The cut surface is bloody and no areas of tubercle formation or consolidation are noted.

Anatomic diagnosis: Primary carcinoma of the right main bronchus; carcinoma invasion of the right lung and mediastinal lymph nodes; tumor compression of the right bronchus and superior vena cava. Bilateral metastatic carcinoma of the adrenal glands; metastatic carcinoma of the periaortic, abdominal, iliac and left femoral lymph glands. Extensive fibrous pleuritis; fibrous obliterative pericarditis.

CASE IV.—J. S., a white male, aged forty-five years, entered the hospital complaining of pain in both shoulders and cough of about two months' duration. Physical examination revealed findings of consolidation in the right lower lobe with compensatory emphysema. The spleen was palpable and the liver was enlarged, nodular and firm. There was marked clubbing of the fingers and toes. Roentgen ray examination of the chest, July 28, 1924, revealed two areas of increased density in the thorax, upper left and lower right thirds. Shadow density was more that of a consolidation than a tumor growth, such as metastases. The hemoglobin was 78 per cent; red blood count, 4,700,000; white blood count, 15,000. No blood was noted in the stools and bile pigments were present. The blood Wassermann was negative, and the sputum was repeatedly negative for tubercle bacilli. During the patient's stay in the hospital an appreciable increase in the size of the liver nodules was noted and he developed a tender swelling in the region of the left zygomatic bone and complained of very severe headaches. On August 18 the patient developed a paradoxical incontinence and the next day died.

Necropsy. The left lung shows hypostatic edema. The right lung crepitates in the upper and middle lobes. The lower lobe is solid and is invaded by gray-white carcinomatous tissue, and there is marked thickening of the bronchi, in one place as much as 5 cm. The carcinoma grossly appears to take its origin from the bronchi of the right lobe and extends peripherally to involve the lung tissue.

Anatomic diagnosis: Primary bronchogenic carcinoma of the lower lobe of the right lung; metastatic carcinoma of the mediastinal lymph glands, liver, kidney, left fourth rib and thoracic vertebra, left zygomatic process, the calvarium and brain and a single perigastric lymph gland; marked pulmonary osteoarthropathy.

CASE V.—W. P., a white male, aged sixty-five years, entered the hospital complaining of pain in the upper right quadrant of the abdomen, weakness, loss of weight amounting to 50 pounds in the past three months and loss of appetite. Physical examination revealed lagging and lessened breathing movements in the upper left lobe with definite dulness in the left supra-

clavicular and infraclavicular spaces. Bronchial breathing was present over the area of dullness with a few rales. The liver was one hand's breadth below the costal margin, hard, nodular and somewhat painful. The axillary glands were enlarged and nodular. The hemoglobin was 92 per cent; red blood count, 5,408,000; white blood count, 10,700. The urine contained a trace of albumin with a few hyaline and granular casts. Roentgen ray of the lungs, October 31, 1922, showed the left apex clouded; upper right lobe showed dense clouding; trachea not displaced; mottling was not proportionate for the extent of the shadow, suggesting that it may not be tuberculous. The blood Wassermann test was negative.

Necropsy. (Dr. Moody.) The right lung is mottled gray-black. No areas of consolidation. Cut surface is gray and moist. The left lung is small and compressed and in the upper lobe there is a tumor nodule 7 cm. in diameter. There are nodules of tumor tissue in the upper portion.

Anatomic diagnosis: Primary bronchogenic carcinoma of the left lung; metastatic carcinoma of the periaortic tissues, liver, left lung, heart and pericardium; compression atelectasis of the left lung; bilateral fibrous pleuritis.

CASE VI.—A. Y., a white male, aged fifty-two years, entered the hospital, February 9, 1924, complaining of cough, bloody expectoration, loss of weight and marked weakness, with pain in the chest of four months' duration. Physical examination revealed flatness over the left lower lobe posteriorly with diminished tactile fremitus over this area and distant breath sounds. Coarse and moist rales were heard over both lungs. There was a spastic paralysis of the left arm and leg with a bilateral ankle clonus and Babinski with increased knee jerks. No rigidity of the neck; no ocular or facial paralysis. The hemoglobin was 45 per cent; red blood count, 3,500,000; white blood count, 12,600.

Necropsy. (Dr. Singer). The left lung is crepitant over the upper lobe and boggy posteriorly. The lower lobe is fluctuant over the lower three-fourths and is airless. Section of this lobe reveals the central portion to be occupied by a soft broken-down mass of tissue, enclosed in a definite capsule. The mass measures 6 by 10 cm. Most of the tissue here is soft and friable, the remainder bloody. Attached to the wall of the vein to the left lower lobe there is a white tumor mass which occludes it. Lung weighs 1200 gm. The right lung crepitates throughout and weighs 640 gm.

Anatomic diagnosis. Primary bronchogenic carcinoma of the left lung; metastatic tumor invasion of the periaortic, tracheobronchial and left bronchial lymph glands; large solitary metastatic tumor nodule of the left adrenal gland; multiple secondary tumor nodules of the brains; left serosanguineofibrinous pleuritis; parietal tumor thrombus of the first portion of the left pulmonary vein; peripheral pneumonia of the left lower pulmonary lobe; acute parenchymatous degeneration of the liver, kidneys and myocardium; hypostatic hyperemia of the lungs.

CASE VII.—W. E., a white female, aged about sixty-nine years, entered the hospital, July 3, 1924, complaining of shortness of breath, swelling of the lower extremities, cough, precordial pain and palpitation all of about four months' duration. In the past she had had repeated attacks of rheumatism. Physical examination revealed the left border of the heart to be 2 cm. outside the nipple line, the right border 2 cm. to the right of the sternum. No murmurs were heard and the tones were regular. The lungs showed dulness over the entire left chest with dullness over the right lung posteriorly. Rales were present over the entire left chest and lower part of the right. There was slight edema of the lower extremities. On July 4

the left pleural cavity was aspirated and 1400 cc. of a hemorrhagic fluid was obtained. This had a specific gravity of 1022, with a predominance of lymphocytes. Cultures showed Staphylococcus albus. The white blood count was 8500.

Necropsy. (Dr. Singer.) The lower portion of one of the primary left bronchi shows mottled white patches, not ulcerated. The mucosa covering it is normal. The left lung is about one-third normal in size and crepitation is absent everywhere. There is one nodule near the base, about the size of a large walnut, whose cut surface reveals white tumor tissue, from which a white material may be readily scrapped. The pleura is thickened and in one place there is a soft fungating mass with a fleshy surface. The remainder of the pleura is nodular and roughened. The right lung crepitates throughout. One small nodule is felt over the lower lobe, which on cut section appears fleshy.

Anatomic diagnosis: Primary carcinoma of the left lung; diffuse tumor invasion of the left pleura; metastatic tumor nodules of both lungs; carcinomatous invasion of the tracheobronchial lymph glands; multiple nodular tumor metastases of the pericardium; left hemothorax; marked compression atelectasis of the left lung; eccentric hypertrophy of the left ventricle; generalized senile arteriosclerosis; moderate dilatation of the right heart chambers; passive hyperemia of the lungs; chronic passive congestion of the abdominal viscera.

Case VIII.—L. W., a white male, aged sixty-five years, entered the hospital, June 20, 1924, complaining of cough, loss of weight and weakness. The cough was of two months' duration, was paroxysmal in character and productive of a yellow-gray mucus and occasionally a small amount of dark brown material, with a foul odor at times. Physical examination revealed impaired resonance posteriorly over the left lower lobe of the lung, with decreased tactile fremitus on the left side. The voice sounds were diminished over the left lobe posteriorly. No changes were noted in the breath sounds. Fine crepitant rales were heard over the left lobe posteriorly. Repeated examinations of the sputum were negative for tubercle bacilli. The hemoglobin was 80 per cent; white blood count, 12,200. Roentgen ray of the chest on June 23 showed obscurity throughout both lungs more in the lower half of the right and lower fourth of the left lung. An even density of the lower half of the right lung suggests an incompletely resolved consolidation. Fleck-like densities of the upper half of the right and upper three-fourths of the left without greater involvement of the apices renders possible tuberculous character. The blood Wassermann was negative.

Necropsy. (Dr. Singer.) The lining of the trachea is everywhere covered diffusely by small nodules about 1 mm. in diameter. In the lower part of the trachea there is a black plaque larger than the others, which is puckered. The left lung is markedly scarred and covered everywhere by thick fibrous parietal pleura, particularly about the apex. There are numerous yellow nodules in the apex and upper lobe. The lower portion of the lung posteriorly is completely consolidated. The right lung weighs 820 gm., and its surface is covered by fibrous parietal pleura. The apex is nodular superficially. Nodules are also found throughout the remainder of the surface of the lung. The lower aspect posteriorly is consolidated. Both lungs contain within their substance white tumor tissue, particularly prominent about the bronchi causing in many places constriction of the lumen. Some of these nodules have undergone softening and consist of white pultaceous matter. The larger bronchi are scarred longitudinally, nodular and their lumen is constricted. This is present on both sides.

Anatomic diagnosis: Primary submucous carcinoma of the trachea with

diffuse bronchial invasion; diffuse carcinomatosis of both pulmonary lobes; tumor infiltration of the visceral and parietal pleuræ with bilateral hemothorax; carcinomatous invasion of the mediastinal lymph glands; secondary nodular carcinomatosis of the pericardium; metastatic carcinomatous nodules of the liver and adrenal glands; hypostatic bronchopneumonia.

CASE IX.—T. S., a white male, aged forty-two years, entered the hospital, August 2, 1924, complaining of pain in the left chest, back, shoulders, elbows and left lower extremity all of three months' duration. Hoarseness and night sweats had been present for three weeks prior to entrance. Loss of weight had been 35 pounds since the onset of symptoms. Physical examination revealed bilateral hard, nonmovable glandular masses in the supraclavicular fossæ. The anterior and posterior cervical nodes were enlarged on the right side. The chest and lungs showed nothing noteworthy. Laryngoscopic examination showed a paralysis of the left vocal cord and paralysis of the left side of the palate. This was ascribed to local pressure on the left recurrent laryngeal nerve. The sputum was repeatedly negative for tubercle bacilli. The hemoglobin was 60 per cent; red blood count, 3,700,000; white blood count, 9600. Roentgen ray of the chest showed the left apex to be veiled. The right apex was obscured by a small shadow extending at the chest periphery into the region dorsal to the first intercostal space, having a convex well-defined border and being of even density. This was thought to be a neoplasm within the lung. Roentgen ray examination of the gastrointestinal tract was negative. Biopsy examination of a gland removed from the neck revealed carcinomatous invasion. The patient refused to stay in the hospital and left in poor condition. This case was diagnosed as primary carcinoma of the right apex with metastases to the supraclavicular and cervical nodes.

CASE X.—J. B., a white male, aged thirty-nine years, entered the hospital complaining of pain in both shoulders. This was constant, dull aching in character and aggravated on coughing and deep inspiration. In addition, cough, weakness, loss of weight and a sharp stabbing intermittent pain beneath the sternum and radiating backward were present. Physical examination revealed the anterior chain of cervical nodes enlarged. The glands were discrete, firm, shot-like and not tender. The chest revealed poor expansion bilaterally. Over almost the entire lung was noted diminished tactile fremitus, flatness, distant tubular breathing, bronchophony and pectoriloquy. The abdomen showed moderate tenderness and slight rigidity in the left upper quadrant. The liver was three fingers' breadth below the costal margin. The hemoglobin was 55 per cent; white blood count, 10,500. The sputum was repeatedly negative for tubercle bacilli. The blood Wassermann test was negative. The condition of the patient was too poor to allow Roentgen ray examination.

Necropsy. (Dr. Singer.) The anterior mediastinum is thickened and contains nodules of tumor tissue. The tumor tissue extends well up into the neck. Along the abdominal aorta are glands containing tumor tissue. There are a number of tumor masses beneath the right parietal pleura. In cutting into the bronchi of the left lung just at the bifurcation there is a tumor nodule obstructing the bronchus to the upper lobe. The upper portion of the left lung contains a number of abscess cavities containing brownish-red fluid. There are a number of similar abscesses in the lower lobe. The upper lobe of the left lung is uniformly consolidated and granular, and for the most part gray, while in the lower lobe are circumscribed areas of consolidation. The right lung is heavy and bloody, containing a large number of raised granular areas.

Anatomic diagnosis: Primary carcinoma of the superior left bronchus

with metastases into the left lung; metastatic carcinoma of the kidneys, adrenals, liver and pancreas; carcinomatous invasion of the superior mediastinal and left cervical tissues; tumor involvement of the cervical, mediastinal and abdominal lymph nodes; secondary carcinomatous nodule in the tip of the appendix; tumor constriction of the bronchioles of the left lung with bronchiectatic cavitation and abscess formation; encysted empyema of the left pleural cavity; multiple disseminated metastatic tumor nodules in the brain; subcutaneous metastatic nodule in the left chest; pneumonic consolidation of the left lung; hypostatic bronchopneumonia of the right lung; bilateral acute fibrinous pleuritis; cloudy swelling of the parenchymatous organs.

CASE XI.—E. D., a white male, aged fifty-seven years, entered the hospital complaining of shortness of breath and cough of six weeks' duration. Physical examination revealed poor expansion, impairment of resonance, tubular breathing, bronchophony and egophony over the left lower lobe. Rales were heard scattered through the right lung. The patient sank rapidly and died, March 11, 1924. The hemoglobin was 80 per cent; white blood count, 17,400.

Necropsy. (Dr. Singer.) Left lung: The surface of the upper lobe is covered by a thick layer of parietal pleura, thickest in the lower half, measuring fully 6 mm. in thickness. The parietal pericardium is attached to the lung. Numerous nodules are felt throughout the upper lobe. On section of the upper lobe and upper two-thirds of the lower lobe the lung is wet, mottled red and black and contains numerous tumor nodules 1 to 3 mm. in diameter. The lower third of the lower lobe is very hard and on section is mottled gray with a small amount of black and has the appearance of firm fibrous tissue or tumor. No caseation is seen, but there are numerous pockets of pus. The upper margin of the tumor is sharply demarcated from the lung by firm fibrous tissue. This is roughly triangular in shape, measuring 9 by 6 by 10 cm. The lung weighs 1000 gm.

Anatomic diagnosis: Primary diffuse alveolar carcinoma of the left pulmonary lobe; carcinomatous metastases to the left upper lobe, the right lung and mediastinal lymph glands; tumor invasion of the liver and right adrenal glands; marked left fibrous pleuritis; diffuse fibrous mediastinitis; marked fatty changes of the liver; chronic diffuse nephritis; right hydrothorax.

CASE XII.—W. R., a white male, aged thirty-eight years, entered the hospital on December 2, 1921, complaining of symptoms which led to a diagnosis of chronic rheumatoid arthritis. The patient left the hospital, but returned, January 3, 1922, complaining of pain in the back and neck and swelling of the wrists and ankles. No chest findings were noted nor were there any complaints referable to the respiratory system. On February 4 the temperature suddenly became elevated to 104.8° and respirations to 26. Examination of the chest revealed dulness, tubular breathing and coarse rales over the right upper lobe. Posteriorly at the angle of the scapula dulness tubular breathing and coarse rales were noted. The hemoglobin was 90 per cent; red blood count, 4,816,000; white blood count, 21,150. The sputum was repeatedly negative for tubercle bacilli. The Wassermann test was negative both in blood and spinal fluid.

Necropsy. (Dr. Moody.) The right lung weighs 400 gm. Under the pleura in the lower lobe there are a number of small white nodules 1 to 3 mm. in diameter, and these are scattered throughout the lower lobe but nowhere else. Crepitation is everywhere present, although there is slight loss of elasticity. On cut section there are a number of small tumor masses in the tissue of the lung. The left lung weighs 1880 gm. The

pleural surface of the upper lobe is everywhere studded with tumor masses. It is quite solid, airless and in the lining of the bronchi there are a number of white tumor masses, particularly in the left bronchus below its bifurcation. Cut surface of the upper lobe shows the lung tissue to be practically invaded everywhere by tumor tissue. The lung is solid and in the region of the larger bronchi there is more tumor than at the periphery.

Anatomic diagnosis: Primary bronchogenic carcinoma of the left lung; metastatic carcinoma of the peribronchial and periaortic lymph glands, right lung, liver, both adrenals, pleura, pericardium and costochondral cartilage of the third and fourth ribs; clubbing of the fingers and toes; compensatory emphysema of the right lung; pathologic fracture of the costochondral junction of the third and fourth ribs; scar of the glans penis; syphilitic aortitis.

CASE XIII.—M. H., a colored female, aged seventy years, entered the hospital, January 27, 1924, complaining of shortness of breath of five weeks' duration, productive and persistent cough, orthopnea and swelling of the ankles of three weeks' duration. At the time of admission the dyspnea was so severe that the patient was unable to speak, was very restless and gasped for air. On physical examination the chest showed a filling out of the intercostal spaces on the right side. Resonance was absent, expansion limited, breath sounds suppressed and tubular, tactile fremitus was absent and voice sounds were suppressed over the entire right chest. The left lung was practically normal. The heart showed a forceful apex beat situated in the eighth interspace in the anterior axillary line. The tones were weak and rapid. No murmurs or thrills were present. The liver extended four fingers' breadth below the right costal margin. There was moderate edema of the ankles. On January 28, 1924, the right chest cavity was tapped and 350 cc. of red-brown fluid was obtained. The hemoglobin was 90 per cent; red cell count, 3,820,000; white cell count, 9880. The urine showed albumin with hyaline and granular casts. The blood Wassermann test was negative. The blood chemistry findings were within normal limits. Roentgen ray of the chest showed obscurity of the whole right lung with displacement of the heart far to the left. The left lung was negative.

Necropsy. (Dr. Singer.) The left lung appears small, moist and red, expecially in its dependent portion where much frothy red fluid can be expressed. The right lung is collapsed against the vertebral column. The outer surface is covered with fibrin. In no portion is it crepitant. It is nodular irregularly throughout. On cutting into the bronchus of the upper lobe a point of constriction is met just beyond the bifurcation of the main bronchus, about which white tumor tissue is seen extending along the bronchus. No distinct ulceration is noted of any of the bronchi. Diffuse deposits of tumor tissue are seen throughout the lung measuring 2 mm. to 2 cm. in size.

Anatomic diagnosis: Primary carcinoma of the right bronchus; tumor metastases throughout the right lung; metastatic carcinoma of the tracheobronchial, bronchial, periaortic, peripancreatic and peribiliary lymph glands; secondary carcinomatous deposits in the liver; right hemothorax; compression atelectasis of the right lung; localized right bronchiectasis; acute right fibrinous pleuritis; healed tuberculosis of the tracheobronchial lymph nodes; fibrous thickening of the apical pleura of both lungs; early metastatic invasion of the left parietal pleura; brown pigmentation of the liver and myocardium; multiple acute ulcers of the duodenum.

CASE XIV.—J. S., a white male, aged fifty years, entered the hospital, March 18, 1921, complaining of pain in the neck and head, pain in the

shoulders and hips, pain in the chest, cough and expectoration. Pain in the chest first started on the left side then shifted to the right side. Physical examination revealed marked tenderness on pressure over the cervicodorsal region of the spine. The lungs showed decreased resonance over the left lower lobe with many mucus rales throughout the chest. The liver was two fingers' breadth below the costal margin. Repeated examinations of the sputum were negative for tubercle bacilli. On May 2 the left chest cavity was aspirated and a bloody fluid was obtained which showed 72 per cent polymorphonuclears and 27 per cent lymphocytes. The blood Wassermann test was negative. The red blood count was 4,064,000; the white blood count, 12,500. Roentgen ray of the chest, April 14, showed moderate amount of diffuse fibrosis in the right lung. The left lung showed similar fibrosis in the upper portion, while the lower lung area was obliterated by greatly increased shadows due partly to a greatly thickened costal pleura. On April 23 Roentgen ray revealed the entire left side occupied by a shadow density characteristic of fluid.

No change was noted in the patient's condition until April 10, when he developed a left-sided anesthesia with also right sided involvement. Neurologic diagnosis was Brown-Sequard paralysis, due either to a vertebral lesion or extradural spinal tumor. Roentgen ray of the cervical spine was negative. On April 26 several small hard nodules were felt in the abdominal wall; one was removed and examined microscopically and showed infiltrating actively dividing cells typical of malignancy.

Necropsy. (Dr. Wells.) May 17, 1921.

Anatomic diagnosis: Primary bronchogenic carcinoma of the left lung with suppurative bronchitis, atelectasis and abscess formation in the left lower lobe; tumor metastases in both adrenals, both kidneys, both iliac bones, right seventh rib with pathologic fracture, left twelfth rib with pathologic fracture, neck of the femur with pathologic fracture and right pleura; solitary metastases in the right lung; subcutaneous metastases in the abdominal wall and both axillæ; two tumor metastases in the left cerebral hemisphere; metastases in the occipital and base of sphenoid bone with compression of the medulla, in the pancreas and in the hilum of left kidney, in the mesentery, in epicardium and in the mesogastric lymph nodes; healed tuberculous scars in both lungs, healed caseous tuberculosis of the right peribronchial lymph nodes.

Case XV.—M. W., a white male, aged fifty-seven years, entered the hospital complaining of a nonproductive cough, pain in the right side of the chest and paroxysmal dyspnea. The duration of these symptoms was five weeks. Painless swelling of the right side of the neck and of the left arm were noted three weeks prior to entrance. Physical examination revealed a marked prominence of the left side of the neck, due to cervical adenopathy, consisting of painless, discrete, hazel-nut-sized glands. The axillary nodes were enlarged more markedly on the right side. The left forearm was edematous. The chest revealed limited expansion especially on the right side. Vocal fremitus was increased on the right side and percussion showed flatness over the entire right lung. Breath sounds were heard with diminished intensity over the right lung. Over the left lung posteriorly from the second to the sixth dorsal spine bronchial breathing, bronchophony and slight egophony were heard. The hemoglobin was 80 per cent; red cell count, 3,150,000; white cell count, 12,000. Roentgen ray of the chest, January 16, 1924, revealed a defective right diaphragm, indefinite cardiac and arch borders, much fibrosis of the right lung with infiltration diminishing toward the periphery on the right. An irregular cavity was noted near the right hilum and deviation of the trachea. Biopsy of a cervical gland showed secondary carcinoma. The patient died Janu-

ary 28; no necropsy was obtained. This case was diagnosed as primary carcinoma of the right lung with metastases to the cervical glands.

CASE XVI.—S. A., a white male, aged sixty years, entered the hospital, September 10, 1922. No history of his complaints could be obtained, because of his inability to speak English. Physical examination revealed slight cervical adenopathy. The right side of the chest appeared larger than the left. Vocal fremitus was slightly increased low down over the left base. Percussion revealed a flat note over the lower lobe. Breath sounds were harsh everywhere except over the left base, where they were heard poorly. Coarse moist rales were present over all parts of the lungs. During the course of the examination the patient expectorated a bloody fluid, dull pinkish in color and foul smelling. No tubercle bacilli were found in several specimens of sputum. Expectoration of large quantities of sputum continued. The hemoglobin was 60 per cent; red cell count, 3,500,000; white cell count, 40,000.

Necropsy. (Dr. Singer.) The right lung weighs 820 gm.; its surface is smooth; crepitates throughout, less in the lower portions. A few solid areas are noted throughout. The lower lobe is dark red and bloody. There are numerous small red raised granular areas solid in consistency. The left lung is covered by numerous fibrous tags. Posteriorly the parietal pleura is adherent. The lower lobe is increased in consistency, and there is definite evidence of cavitation. On section the upper lobe is solid, red and fleshy. The lower lobe is replaced by a cavity filled with dirty gray fluid with thrombosed vessels coursing through it. The walls are firm and appear fibrous. There is a large patent bronchus leading to this cavity.

Anatomic diagnosis: Primary ulcerating carcinoma of the left bronchus with metastases to the left lung and to the tracheobronchial lymph nodes; huge abscess cavity of the left lower pulmonary lobe; compression atelectasis of the left upper lobe; bronchopneumonic foci of the right upper lobe; marked hypostatic hyperemia and edema of the right lower lobe; marked senile sclerosis of the aorta with atheromatous ulceration and calcification; partial obliterative left fibrous pleuritis.

CASE XVII.—J. B., a colored male, aged fifty years, entered the hospital, December 26, 1920, complaining of weakness, dyspnea and coughing of blood of four months' duration. Physical examination was essentially negative except for the findings of a pleural effusion over the entire right chest. Paracentesis thoracicis revealed a straw-colored fluid; specific gravity, 1013; 75 per cent polymorphonuclears and 25 per cent lymphocytes and no bacteria. The Wassermann tests of both the blood and spinal fluid were negative. Roentgen ray showed extensive pleural exudate on the right side with the entire left thorax of normal appearance.

Necropsy. (Dr. Wells.) The right lung does not collapse and is very heavy, weighing 2400 gm. with the trachea. The lower lobe is completely and uniformly consolidated, except at its inferior margin; the upper lobe is also consolidated except the anterior fourth. The densest consolidation in all of these is nearest the hilum. This consolidation is uniform except on the surface, where it is nodular. Opening into the right main bronchus finds it completely plugged to within 15 mm. of the bifurcation by a mass of necrotic tissue. The mucous membrane about this is reddened. Cut section shows a diffuse grayish consolidation, with areas of suppuration in the peripheral portion. There are white tumor nodules in the middle lobe. In the upper lobe there is a mass of white tissue involving the hilum of the lung and continuous with the necrotic mass in the main bronchus.

Anatomic diagnosis: Primary bronchogenic carcinoma of the right main

bronchus with metastases in the left lung; metastases in the mediastinal and cervical lymph glands, left kidney and sixth left rib with pathologic fracture; subcutaneous metastases over the third left costal cartilage and left parietal pleura invading the pericardium; unresolved suppurative bronchopneumonia of the right lower and middle lobes; right serofibrinous pleuritis; left hydrothroax; acute and chronic vegetative mitral endocarditis.

Case XVIII.—A. P., a white male, aged thirty-three years, entered the hospital, February 7, 1923, complaining of dyspnea, cough and expectoration of foul-smelling brownish sputum. In addition, loss of weight and strength was also complained of. The physical examination revealed the right eyelid to be markedly swollen and the left eyelid less so. The nose was also involved in the swelling. The neck was swollen and puffy and there was a similar swelling over the sternum. The respirations were labored. Over the left chest the percussion note was hyperresonant, the breath sounds were increased and tactile fremitus was increased. Over the right chest dulness was elicited inferiorly with hyperresonance at the clavicle, cavernous breathing was heard just below the clavicle. The heart was negative.

Necropsy. (Dr. Singer.) The left lung weighs 1500 gm., is greatly enlarged and boggy. The cut surface is wet and at the posterior portion of both lobes there are a number of raised granular areas. The right lung is tightly adherent to a large irregular mediastinal mass. The pleura over it is thickened to 3 mm. On cut section of the lung there is a large amount of tumor tissue in the lower portions of the upper lobe, measuring 9 by 6 cm. The remainder of the upper lobe is firmly consolidated and from its surface and from cavities communicating with its bronchi a foul smelling purulent fluid can be expressed. The lower lobe is partially consolidated, especially in the posterior portions. In the anterior portion there are a number of cavities which almost entirely replace the parenchyma with necrotic lining, three of which measure 4 cm. in diameter. Attached to the lung in the anterior mediastinum is a firm nodular mass of tumor tissue, through which the superior vena cava courses and a large sound is passed through with only slight difficulty. This tumor mass measures 11 by 10 cm.

Anatomic diagnosis: Primary bronchogenic (?) carcinoma of the right upper lobe with metastases in the mediastinal glands and tissue with partial obstruction of the superior vena cava; bronchiectasis and bronchiectatic cavitation of the entire right lung; pneumonic consolidation of remainder of right upper lobe and anterior portion of lower; right fibrous obliterative pleuritis; edema of tissues of head and neck, upper thorax and upper extremities; varices of superficial veins of both shoulder regions.

Case XIX.—F. S., a white male, aged forty-four years, entered the hospital, November 9, 1919, complaining of cough, hemoptysis, dyspnea, weakness, pain in the chest and loss of weight. These symptoms were about of two months' duration. Physical examination showed partial consolidation of both upper lobes posteriorly and the right upper anteriorly. Rales were heard over the remaining portions of the lungs. The liver was 6 cm. below the costal margin and the extremities showed slight osteoarthropathy. The sputum was repeatedly negative for tubercle bacilli. Roentgen ray of the chest showed a dense mass shadow in the left hilum extending in all directions into the lung area. While not definitely circumscribed, this had the appearance of a tumor of the hilum.

Necropsy. (Dr. Wells.) The upper lobe of the left lung is infiltrated with tumor tissue in about two-thirds of its extent reaching in places to the pleura. At the lower margin of the left upper lobe there is a pus-filled

cavity lined with a pyogenic membrane. There is another area of softening nearly black in color and another of beginning suppuration. The tumor extends along the large bronchi and vessels about 5 cm.; from there to the periphery the upper lobe is largely consolidated. The lower lobe is boggy and full of fluid with only a few small areas of bronchopneumonia. The extension of the tumor within the lung is in the form of dense white tissue growing from the hilum into the upper but not the lower lobe. The tumor has invaded the main left bronchus at the origin of the superior division. The bronchus here is nearly occluded and the mucosa ulcerated. The right lung is free from tumor tissue and shows only an area of hypostatic bronchopneumonia.

Anatomic diagnosis: Primary bronchogenic carcinoma of the left upper lobe of the lung; metastases in the liver, thyroid, bones, spleen, adrenals, right kidney, left tonsil, tongue, trachea, ileum, appendix, pancreas, neck of the gallbladder; extensive infiltration of the cervical, mediastinal and retroperitoneal lymph glands; gangrene and abscess formation in the left upper lobe; hypostatic edema and bronchopneumonia of both lungs; fatty infiltration of the liver.

CASE XX.—C. S., a white male, aged thirty-one years, entered the hospital, March 15, 1917, complaining of severe frontal headache, failing of vision in the right eye, cough, loss of weight and night sweats. Headaches had been present for the past two years, while the other symptoms had been only of six months' duration. Physical examination showed that the pupils reacted sluggishly to both light and accommodation. There was limited expansion over the left side of the chest. Over the right lower lobe flatness with absent breath sounds was noted. The heart was displaced to the right, but otherwise was normal. Findings were present of a left-sided hydrothorax. Repeated puncture of the chest showed a serous hemorrhagic fluid much less than was expected. The blood Wassermann was negative.

Roentgen ray examination of the chest revealed a very dense shadow in the left lower lobe, the outline of which was smooth and rounded. It was centrally located, the outer portion of the lung area being very clear. This was thought to be a tumor. Subsequent examinations corroborated this finding.

Necropsy. (Dr. Nuzum.) The left pleural cavity is completely obliterated by fibrous adhesions. There is a walled-off cavity containing pus. The left lung weighs 1800 gm. The pleura covering it is dull, opaque and thickened throughout. The lung is uniformly solid, no single nodular areas being palpable. On cut section it is difficult to ascertain where the tumor growth arises, although it appears to extend from the larger bronchi. The left lower lobe is extremely firm, except for various areas which have undergone softening. These contain purulent material. The right lung shows numerous areas of bronchopneumonia with marginal emphysema.

Anatomic diagnosis: Primary bronchogenic carcinoma of the lower lobe of the left lung; left-sided obliterative fibrous pleuritis; metastatic carcinomatosis of the peribronchial and periaortic lymph nodes; disseminated pseudolobar bronchopneumonia; mucopurulent tracheobronchitis; marginal emphysema of the right lung; passive hyperemia of the liver and spleen; cloudy swelling of the myocardium; fatty changes of the liver and kidney.

CASE XXI.—A. W., a white male, aged thirty-six years, entered the hospital, July 22, 1918, complaining of cough, dyspnea, loss of appetite and loss of weight. His illness was of but six weeks' duration. Physical examination revealed flatness over the left lung with some suppression of the breath sounds. Sibilant and moist rales were heard over the right

lung. On August 18 the left chest cavity was tapped and much pus was obtained. The white cell count was 30,000. The sputum was repeatedly negative for tubercle bacilli. Roentgen ray examination of the chest showed obliteration of the lung shadows of the left chest as high as the clavicle. The heart shadow could not be distinguished. The esophagus was crowded slightly to the right and forward and was pressed upon sufficiently to cause temporary obstruction and dilatation three fingers' below below the sternal notch.

Necropsy. (Dr. D. J. Davis.) The right lung is normal except for fibrous tags on its surface. The left lung surface is studded with numerous white nodules, varying from the size of a pinhead to 5 cm. in diameter. White masses extend through the mediastinum. Cut surface reveals numerous similar nodules, more numerous about the hilum and lower portions of the lung. Retention abscesses are seen which exude green slimy pus. The bronchial tubes are greatly thickened and exude pus. A large mass is situated just below the bifurcation of the trachea which presses upon and involves the left main bronchus.

Anatomic diagnosis: Primary carcinoma of the left bronchus; secondary carcinoma of the lungs, pleura, mediastinal tissues and pericardium; metastatic carcinomatous nodules in the capsule of the liver; retention abscess in the parenchyma of the left lung; bilateral fibrinous pleuritis; massive anemic infarcts of the spleen and both kidneys; thrombosis of the branches of the hepatic artery; left-sided seminovesiculitis; rupture of a metastatic carcinomatous nodule into the general peritoneal cavity.

CASE XXII.—F. J. D., a white male, aged forty-five years, entered the hospital, June 1, 1921, complaining of cough, loss of weight, weakness and loss of appetite. His illness was of eight months' duration. Physical examination revealed impaired resonance over the left lower chest posteriorly below the level of the seventh dorsal vertebra, extending outward to the midaxillary line. Breath sounds diminished over this area of dulness. Crackling rales were heard over the left apex. There were no findings over the right lung. Roentgen ray examination revealed a shadow in the left lower thorax, indicating pleural pathology. The blood Wassermann test was negative.

Necropsy. (Dr. Wells.) The left lung is completely collapsed. Its pleura is everywhere thickened to about 1 to 3 mm. On palpation the lung has a water-logged, rubbery feel. On cut section of the upper lobe a diffuse mass of cancerous tissue, 6 cm. in diameter, surrounds the left bronchus and bronchioles. The lining of the bronchus is roughened and cancerous ulcerative tissue can be seen in the lining. The lower lobe on section is found filled with dark green, very foul smelling pus. The right lung is normal except for congestion.

Anatomic diagnosis: Primary bronchogenic ulceromedullary carcinoma (left), with metastases to the tracheobronchial, periesophageal, perigastric, peripancreatic lymph glands; metastatic carcinoma of the liver and dura mater; left-sided empyema with complete atelectasis of the left lung; abscess of the lower lobe of the left lung; marked left-sided fibrous pleuritis; hypostatic hyperemia and edema of the right lung; marked dilatation of the stomach due to hemorrhage into it; pachymeningitis externa.

CASE XXIII.—S. W., a white male, aged fifty-five years, entered the hospital, August 3, 1924, complaining of pain in the left hip of four months' duration, and in addition loss of weight. Physical examination revealed an enlarged submaxillary and posterior cervical node on the left side. The glands were firm, discrete and movable. The lungs showed flatness over the entire left chest anteriorly and posteriorly as high as the third

dorsal spine with impaired resonance above this. Bronchial breathing was present over the left apex posteriorly, while the breath sounds were absent over the lower anterior and posterior chest on the left side. Tactile and vocal fremitus was absent over this region. There were a few moist rales over the right base posteriorly. There was bilateral inguinal adenopathy, and marked tenderness was present over the left iliac crest. Pain was elicited on moving the left leg and swelling was noted below the left iliac crest and over the great trochanter. The blood Wassermann was negative and the sputum was repeatedly negative for tubercle bacilli. Aspiration of the left chest cavity revealed a yellow-brown serous fluid, which contained a great number of lymphocytes and erythrocytes. The white blood count was 14,000; red cell count, 3,800,000; hemoglobin, 80 per cent. Roentgen ray examination of the chest showed the heart displaced to the left slightly, indicating much fibrosis, despite the fact that a fluid level of hydro-or pyopneumothorax was seen at the height of the first intercostal space, which with pleural thickening obliterated the rib shadows.

Necropsy. (Dr. Rappaport.) The left lung weighs 1200 gm. with attached pleura. Its surface is covered with thick fibrous pleura. Crepitation is absent, the lung being nearly solid. Cut surface reveals mottled yellow-white and black surfaces and consolidation, except for the apex and portions of the inferior lobe. The right lung crepitates throughout and its cut surface appears grossly unchanged.

Anatomic diagnosis: Primary diffuse carcinoma of the left upper lobe; nodular carcinomatous metastases to the left pleura; left serofibrinous pleuritis with compression atelectasis of the left lower pulmonary lobe; carcinomatous metastases to the iliac crests; metastatic carcinoma to the tracheobronchial, cervical and axillary nodes; miliary disseminated carcinomatous nodules of the epicardium and peritoneum; nodular carcinomatous metastases to the liver and kidneys; solitary ulcerating carcinomatous nodule of the ileum; right focal fibrous pleuritis.

Case XXIV.—J. C., a white male, aged fifty-five years, entered the hospital, February 11, 1920, complaining of pain in the right arm and scapular region for the past eight weeks; cough productive of blood-tinged sputum of one week's duration and night sweats for one week. Loss of weight, loss of appetite and weakness were also complained of. Physical examination revealed the cervical chain of glands on the right side definitely enlarged. The left lower lobe of the lung was dull, and breath sounds were diminished. Posteriorly over the right upper lobe resonance was diminished and breath sounds were exaggerated. The heart was enlarged in all diameters and the tones were faint, but regular. There was spasm and tenderness of the right trapezius, with atrophy and weakness of the right hand. This indicated pressure on the brachial plexus by the enlarged cervical nodes. The white blood count was 18,000, and the sputum was repeatedly negative for tubercle bacilli. Roentgen ray examination revealed a disappearance of the transverse process of the seventh cervical vertebra on the right side, suggesting a metastatic malignancy at this point. The thorax contained a marked shadow density situated in the left hilum area extending outward into the lung. Biopsy examination of a cervical gland showed a mass of infiltrating carcinoma cells. The patient was given a few Roentgen ray treatments for carcinoma of the lung. His complaints continued without improvement and against advice he signed a release and left the hospital.

This case was diagnosed as primary carcinoma of the lung (left) with metastases to the cervical nodes and seventh cervical vertebra.

Summary and Conclusions. Primary carcinoma of the lung is not as rare a clinical condition as has been described in the past, and the condition can be diagnosed antemortem.

The striking increase in the number of tumors of the lung since the influenza epidemic suggests some relation between these two conditions.

Pulmonary cancer presents a very varied pathologic picture, not only as to gross and microscopic characteristics, but also as regards the associated pathology.

Metastases occur early and are very widespread.

Histogenesis presents many difficulties, because of the morphological variations in the cells concerned and the difficulty in obtaining the tumors in the early stages for study.

Efforts to classify these tumors as to histogenesis admit great probability of error. However, from authentic studies it appears that origin from bronchial mucosa is most frequent and that origin from alveolar epithelium is very rare.

There are no pathognomonic symptoms of tumor of the lung; weakness, cough, expectoration, pain in the chest and dyspnea being most important.

With more frequent use of the bronchoscope and with an appreciation that primary carcinoma of the lung is not rare, this clinical entity will be diagnosed more commonly antemortem.

The use of the bronchoscope both for diagnosis and treatment opens a field in a condition where formerly the prognosis was very poor.

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REVIEWS.

THE NORMAL DIET. By W. D. SANSUM, M.S., M.D., Director of the Potter Metabolic Clinic, Department of Metabolism, Santa Barbara Cottage Hospital, Santa Barbara, Calif. Pp. 72; 1 illustration. St. Louis: C. V. Mosby Company, 1925.

IN this work the author attempts a brief exposition of "the fundamental principles of diet for the mutual use of physicians and patients." In a work as brief as this the author might better have omitted Chapter IV, entitled "Acidosis," containing, as it does, little of proven value and much which is, to say the least, controversial. It has never been proved, for example, that an acid dietary is a factor in producing migraine or bloodvessel and kidney disease. Again the emphasis which the author places on the neutralization of foods producing an acid ash by alkaline ash foods seems hardly justifiable in the light of what is known of the "buffer" action of the blood. In the remaining chapters the requirements of the body with respect to protein, bulk, water, minerals, vitamins and total calories are dealt with in a far more satisfactory manner. J. A.

TREATMENT OF KIDNEY DISEASES AND HIGH BLOOD PRESSURE. Part I. Practical Manual for Physicians and Patients. By FREDERICK M. ALLEN, M.D., Director of Physiatric Institute, Morristown, N. J. Pp. 206. Newark, N. J.: Newark Printing Company, 1925.

THIS book is an exposition of the author's own views on the treatment of kidney disease and its manifestations. He considers the subject under three headings—nitrogen retention, edema and high blood pressure. He advocates for the first a low protein diet and for the last two a salt-free diet. His discussion of nitrogen retention and of edema is in the main consistent with the views of other students of kidney disease. His views as to the causation and treatment of high blood pressure have not yet received general confirmation from other workers in the field. His directions for giving low protein and salt-free diets are the most useful features of the work. The book contains, however, many dogmatic state-

ments, the accuracy of which cannot be accepted as established, and this detracts seriously from its value and is especially objectionable if the book is to be placed, as its title suggests, in the hands of patients who are without any basis for discriminating between hypothesis and established fact. J. A.

I. The Electrochemical Factor in Neurology. By Ernest H. Pasqué. II. New Concepts of Physics. By Calvin Samuel Page. Pp. 604; 23 illustrations. Detroit: Atomic Research Association, 1925.

The nature of this volume will be apparent, without further comment by the reviewer, from the following typical quotation (p. 476): "Rx is heat; currents of Rx are electricity; Rx is the sustaining force of the atmosphere; the lungs are the dynamo of the body and, collecting Rx from the air, they create the electrical currents that supply the heat and nervous force of animal life." M. J.

A Textbook of Pathology: General and Special. For the Use of Students and Practitioners. By J. Martin Beattie, M.D., Professor of Bacteriology, University of Liverpool, etc., and W. E. Carnegie Dickson, M.D., Pathologist to the West End Hospital for Nervous Diseases, London, etc. Third edition. Pp. 1103; 499 illustrations and 17 colored plates. St. Louis: C. V. Mosby Company, 1925. Price, $11.00.

The thirteen chapters of the first part of this book are on general pathology, and occupy slightly less than one-half the volume. They treat the conventional topics of retrogressive changes, atrophy inflammation, tumors, parasites and so forth in a sound conventional manner. In the same way the twelve chapters of the second part on special pathology discuss the diseases of the various tracts in the customary anatomic sequence of systematic textbooks of pathology. Nor is this treatment without advantage to students, fresh from their anatomic studies, as long as they realize that the subject of pathology may have other methods of approach and that the field of morbid anatomy thus covered is far from comprising the whole subject of pathology. The one hundred and five pages on parasites reflect the progressive and accurate activity of the British in this field. The bone marrow, too, as one would expect from the junior author, receives more adequate attention than is customary in pathologic textbooks, especially in the beautiful colored plates.

But few errors, scriptural and typographical, have been observed. On p. 513 the streptococcus of subacute bacterial endocarditis is designated "hemolytic" instead of "viridans." The reference to Plate XIV on p. 652 should be Plate XIII. Some of the colloquial English terms, for example, "hard-bake spleen" for multiple focal caseous tuberculosis of that organ will be useless for American readers; neither would the reviewer retain "primary splenomegaly" as a synonym for splenic anemia; but these are unimportant details. For this edition the two original volumes, General and Special, "have now been published both separately and also incorporated into a single volume." The reviewer's copy, which falls into the latter category, seems of perfectly usable size. E. K.

THE PHYSIOLOGY OF MIND. By FRANCIS X. DERCUM, A.M., M.D., PH.D., Professor of Nervous and Mental Diseases, Jefferson Medical College, Philadelphia. Second edition. Philadelphia and London: W. B. Saunders Company, 1925. Price, $3.50.

AN interestingly written book, the "object and scope" of which "is to present the basic facts of those reactions of the organism to the environment" which constitutes "mind."

Beginning with most primitive responses of protoplasm, more elaborate mechanisms of receiving and transmitting "impacts" are traced through their development to the complex nervous systems of higher mammals. Psychology of man is presented together with a final appendix on Freudism, which is termed "puerile."

Perhaps some principles of transmission of impacts by means of synaptic contacts should be stated more conjecturally, but the whole is a scholarly presentation which commands deep respect and enriches the intellect of the reader. E. B.

TEXTBOOK OF DIFFERENTIAL DIAGNOSIS OF INTERNAL MEDICINE. By M. MATTHES, M.D., Professor of Medicine and Director of the Medical Clinic, University of Königsberg. Authorized translation of the fourth German edition, with extensive additions by I. W. HELD, M.D., and M. H. GROSS, M.D., New York City. Pp. 908; 176 illustrations, some in color. Philadelphia: P. Blakiston's Son & Co., 1925.

THIS work should be particularly valuable for the practitioner, as well as the internist and student. It presents the subject in a clear, logical, adequate manner; the positive characteristics of a

disease are first described and then the various conditions with which it might be confused are enumerated and the differentiating points explained. The translators have made many valuable additions to the work, bringing it up to date, as well as expressing current American views. The translation, for the most part well done, is open to some minor criticisms. There has been undue adherence at times to the original in the matter of German idiom, with, as a result, unidiomatic English. There are used many Latin terms, so common in German medical writings, but which seem stilted and out of place in English when substituted for well-known English words, as "typhus abdominalis," "lepra," "tertiano," "quartano," "colica mucosa," "porta" of entrance, and the like.

R. K.

SELECTED PAPERS: SURGICAL AND PATHOLOGICAL. By F. T. PAUL, D.Sc., (LIVERP., HON. CAUS.), Ch.M. (LIVERP.), F.R.C.S. (ENG.), Consulting Surgeon, Liverpool Royal Infirmary. Pp. 284; 23 illustrations. London: Baillière, Tindall and Cox, 1925.

TWENTY-TWO miscellaneous contributions to surgery and pathology collected by the author's colleagues on the occasion of his seventy-fifth birthday.

E. K.

THE ART OF MEDICAL TREATMENT. By FRANCIS W. PALFREY, M.D., Visiting Physicians, Boston City Hospital; Instructor in Medicine, Harvard University. Pp. 463. Philadelphia and London: W. B. Saunders Company, 1925.

THE advent of a medical mentor willing to point the nuggets from that greatest of treasures, his own experience, is an event which the student, intern and young physician will hail with keen pleasure.

Prognosis and "what to tell the family" is the bugbear of the inexperienced. Realizing this, the author has undertaken to point out in each disease what information should be imparted to the patient and what to the responsible relative or friend. The author truly propounds the art of treatment of patient and anxious relation. In every paragraph devoted to this subject the reader may find a concise, thoughtful and well-weighed statement of the prognosis to be expected in the light of modern treatment.

In the matter of treatment there is no radical departure from that which is accepted as standard by modern textbook writers. Some of the gastrointestinal therapy excludes modern methods one might expect to see there, on the basis that the older ones have proved

just as effective in the author's hands. The thoughts on stimulation, diet quackery and cults are far too fine to be relegated to the unused limbo of "appendices," and should, we feel, precede the portions dealing with treatment of systemic diseases.

The book represents a splendid balance between common sense and modern medical practice. It should be voluntarily on the young practitioner's desk and by compulsion on that of the senior medical student. C. L.

WILLIAM CADOGAN (HIS ESSAY ON GOUT). By JOHN RUHRÄH, M.D., Professor of Diseases of Children, University of Maryland. Pp. 114; 1 illustration. New York: Paul B. Hoeber, 1925. Price, $1.50.

REPRINTED with corrections from the *Annals of Medical History* of last March. The text of Cadogan's *Essay* is preceded by some biographic notes and succeeded by Mrs. Ireland's poetical review, "The Doctor Dissected, or Willy Cadogan in the Kitchen." One regrets the initial split infinitive. E. K.

ARTIFICIAL SUNLIGHT AND ITS THERAPEUTIC USES. By FRANCIS H. HUMPHRIS. Second edition. Pp. 203. Oxford Medical Publications, 1925.

THIS book is on the whole a very good survey of the general field of ultraviolet therapy for the practitioner. The technical descriptions, making allowance for the fact that the apparatus described is of British rather than American manufacture, are sufficiently detailed to be usable and contain many excellent points with reference to the standardization of equipment, measurement of degrees of reaction, etc. The therapeutic sections of the book reflect perhaps a little too much the optimism which actuates workers in a new field. It is to be regretted that no more satisfactory quantitative measurement of short wave-length dosage than that provided by distance and time is available. The author notes, but has no observations to assist in estimating, the decline in output of quartz lamps under continued use. The range of therapeutic applicability, according to the author, is practically immeasurable, and brief paragraphs are given to everything from ptyriasis (*sic*) to old age. But it is an injustice to speak too ironically of the enthusiasm of a worker in a virgin field, especially when he has written a serviceable little book containing many valuable experimental and technical points for workers with this extremely important therapeutic agent. J. S.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Factors in Causation of Gall Stones.—According to MOYNIHAN (*Brit. Med. J.*, 1925, **1**, 393), the two factors necessary for the causation of gall stones are infection and an increased amount of cholesterol in the blood. Infection may be in the accessory sinuses, the teeth, any part of the digestive or urinary tracts or in extraäbdominal foci. If the infection is brought by the bile the mucosa is first attacked; if by the blood, the submucosa; if by the lymphatics, the serous coat. The author believes that infection of the gall-bladder wall always precedes gall-stone formation. In 100 consecutive cases cultures showed Bacillus coli to be present 48 times; streptococci, 8; double infection, 5; Bacillus pyocyaneus, 2; other organisms, 33. The infection causes a mucous catarrh, with stagnation deposition of the relatively translucent cholesterol and gradually of calcium. The solitary stones of pure cholesterol are not considered to be due to infection. In the examination of the gastric contents of 77 cases, achlorhydria was found in 17; hypochlorhydria in 3, a low normal acidity in 14, normal in 18, high normal in 8 and hyperacidity in 17. Chauffard's low-cholesterol diet is used, that is, skimmed milk, milk and vegetable soup, rice, macaroni, tapioca and so forth, white and lean meat, nonoily fish (boiled or baked), cereals, potatoes (not fried), green vegetables and mild cheeses.

End Results in Splenic Anemia With and Without Splenectomy.—HANRAHAN (*Arch. Surg.*, 1925, **10**, 639) has studied 35 cases of splenic anemia (22 of which had had splenectomy performed) from the points of view of etiologic factors, characteristic blood pictures, duration of symptoms, prognosis and early and late effects of splenectomy. Cases with suggested causes, such as syphilis (4), malaria (7), tuberculosis and other infections, were included, as it was felt by the author that pictures indistinguishable from the splenic anemia of unknown etiology

were produced. The unsatisfactory results of studying the morbid anatomy of splenomegalies is emphasized, the changes in all fibrotic spleens being very similar. Dividing the patients into two groups, (1) those acutely ill with symptoms referable to the anemia and (2) those presenting the picture of a chronic process, the author found that the first group might last from six to eighteen months, with fatal outcome, uninfluenced by splenectomy. In the second group splenectomy is of value, though this type of disorder is not invariably fatal without the operation, and it does not always cure the condition. In the non-operative cases the higher the color index, and the more marked the leukopenia, the worse the prognosis. In the splenectomized cases the color index seems to be immaterial, but not the leukopenia.

Systemic Liver-spleen Disease.—HANAU (*Monatsschr. f. Kinderh.*, 1924, **29**, 54) considers that a liver-spleen syndrome of constitutional origin may follow cirrhosis of the liver in children, due in turn to some congenital anomaly. He describes 4 such cases (3 of which came to autopsy), and discusses 30 culled from the literature. Their ages were two and twenty-one months, eleven and fourteen years. In 3 the abdomen had been known to be large since birth, with big liver and spleen, and jaundice during the first three months of life. In the oldest patient the trouble began at the age of twelve years, after influenza; temporary improvement followed irradiation of the spleen, but soon the picture of Banti's disease supervened together with speech disturbances and paralyses. Autopsy failed to reveal the nature of the disorder.

SURGERY

UNDER THE CHARGE OF

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Intravenous Use of Metallic Mercury (Mercodel) in the Treatment of Syphilis.—ROTHWELL and MALONEY (*Am. J. Syph.*, 1925, **9**, 413) state that intravenous injection of metallic mercury suspensions produce prompt clinical response in syphilis. There is no serious danger in their use, no apparent harm to the vital organs being noted. If used in small doses, 5 cc., the only reaction, if any, is a mild stomatitis. In larger doses, however, a severe stomatitis is produced in some cases. Properly administered, no phlebitis or vein thrombosis results. Primary, secondary, tertiary and cerebrospinal luetic signs have resolved under their use even when used alone. A persistently positive Wassermann has been changed even to a negative or reduced in strength of reaction. A positive spinal fluid has been changed to a negative with reduction of 37 cells to 6 cells. They do not impair the liver or kidneys.

Larger quantities of mercury may be safely administered in a shorter time than in the use of the soluble salts of mercury. No evidence of cumulative effect was elicited in twenty-two months' study of their use in a series comprising 805 injections.

Ununited Fractures.—Groves (*Lancet*, 1925, **209**, 735) says that the causes of nonunion may be grouped as mechanical, vascular (including sepsis, sclerosis of bony canals and atrophy) and disease including infection, pyogenic or specific and new growth. In the varieties of nonunion the author gives delayed union from mere cellular inactivity and definite nonunion from fibrous union (fibrous tissue or fibrocartilage between and connecting the bone ends); nonunion from pseudoarthrosis (bone ends eburnated and covered with fibrocartilage, a joint cavity with capsule and synovial fluid between the ends of the bones); nonunion from gap fracture (a piece of bone lost, the bone ends held apart by the companion bone). The bone is usually thin and atrophic. In the nonoperative methods the author writes on voluntary movements, the fracture being protected with a splint; second, on passive congestion with massage; third, on injection of blood or blood products in and around the fracture. Open operative treatment is advised whenever union has been delayed for more than twelve months, or when there is increasing mobility between the fragments associated with a Roentgen-ray picture of rounded bone ends separated by a definite gap. Methods of stimulating the bone ends are discussed. Shaping and fitting operations are given. The author finally states that the ideal and obvious method of treating ununited fractures is by putting in a bone graft. The causes of failure in this procedure are inadequate contact of bone ends, inadequate fixation of the fracture either by a constructive operation, graft or splint, inadequate splinting of the limb after operation and excessive tension.

Neoplasms of the Blood Lymph-vascular System.—Pulford (*Ann. Surg.*, 1925, **82**, 710) states that a histologic study of the neoplasms of the blood lymph-vascular system of 290 patients treated at the Mayo Clinic shows 183 angiomas, 9 angioendotheliomas and 8 endotheliomas. This simple classification seems adequate to meet all the clinical facts of the cases as well as all the known data from the standpoint of embryology, morphology, situation and "reserve-cell" diagnosis. Endothelium in the embryo is derived from mesenchyme. In adult tissues, although not yet identified, the same mesenchymal cell lying invisible seems most likely to be the reserve cell of endothelium. Endothelium is closely linked with fibrous connective tissue in that mesenchyme is their common ancestor. This relationship does not preclude the existence of a specific tumor of endothelium, distinct from a fibrosarcoma. The study of angiomas led to the recognition of the origin of the malignant tumors of this series from vascular endothelium. A case reported shows the change from benign to malignant in different stages. These original hypotheses seem established as facts: Blood-vascular and lymph-vascular angiomas, while usually benign, are potentially malignant endotheliomas. There is an intermediate stage between these two represented by the angioendothelioma, which is relatively benign, but definitely malignant, and malignant endotheliomas of the blood lymph-vascular system exists as a pathologic entity.

Administration of Iodin in Exophthalmic Goiter.—Rienhoff (*Bull. Johns Hopkins Hosp.*, 1925, **37**, 285) says that iodin produces definite and striking changes in the histologic structure of the thyroid gland in cases of exophthalmic goiter. These changes were: Increase in size of the thyroid gland as a whole, decrease in vascularity and probably in the lymph flow through the gland, a large increase in amount of fibrous connective tissue, a striking increase in amount of colloid deposited and contained within the thyroid gland, a change in the acini from lacelike papillomatous ingrowths to round, even-walled, smooth acini, regular in size and form, and the presence of many mitotic figures before the use of iodin and their absence after the iodin has been given. The clinical improvement and the lowered rate of basal metabolism are directly associated with the change from a typical histologic picture of exophthalmic goiter to a resting colloid stage. In comparing the histologic structure of the thyroid gland in 30 cases of exophthalmic goiter, 15 in which iodin had been given and 15 in which no medication whatsoever had been used, it was observed that the histologic picture following the administration of iodin was constant. An artificial remission of signs and symptoms is produced by iodin. A remission in a case of exophthalmic goiter is associated with a change in the histologic picture from a hyperplastic to a colloid state, even though there is definite evidence of hyperplasia remaining. It is a question of relative hyperplasia.

End Results in Neurosurgery.—Sharpe (*Ann. Surg.*, 1925, **82**, 684) writes that his impression of the end results, from the standpoint of the ability of the patient to earn a living and to be a useful member of the community has been discouraging, and particularly is this true of those patients having had lesions of the central nervous system, such as brain tumor, brain abscess, chronic brain injuries and internal hydrocephalus, whereas more encouraging results have been obtained in the operative treatment of trifacial neuralgia, lesions of the spinal cord, bronchial plexus and of the peripheral nerves, external hydrocephalus in its milder forms, chronic brain injuries of supracortical hemorrhage and then, possibly the most gratifying of all, the treatment of acute brain injuries both in the newborn and in adults. The factor of better teamwork between the neurologist and the surgeon is making possible earlier diagnosis and more accurate localization of the lesion. The surgeon knows what can be done and what cannot be done safely, and in this manner the catastrophies of the past are being avoided. The highly discouraging field consists of brain tumor, brain abscess and the condition of internal hydrocephalus. Fortunately the encouraging field consists of the larger number and of the more frequent neurologic conditions amenable to surgery. The older the patients at the time of the intracranial hemorrhage, the less marked are the gross physical and mental impairments, but the more marked are the subjective complaints, such as headaches, dizziness, early fatigue and changes of personality and the greater are the emotional and psychic impairments. The ideal time for the treatment of brain injuries in both infants and adults is at the time of the acute condition, when the intracranial hemorrhage can be drained.

PEDIATRICS

UNDER THE CHARGE OF

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Should the Schick Test be Abandoned?—KELLOGG (*Am. J. Pub. Health*, 1925, **15**, 868) made observations that showed that the Schick test is subject to many errors in its application, that more than offset the value of the information derived from its use. A high percentage of false negative Schick tests has been found in persons following immunization, the information as to their true status having been determined by laboratory tests using the Kellogg method. The Schick test is of academic interest only, and should be abandoned completely, for the following reasons that the author gives: It is subject to a sufficient percentage of false negative readings to result in the failure to protect children who otherwise would have been protected. Knowledge of the immune status of children is not required, as most of the age groups most concerned are susceptible, while immunization of the balance is open to no objection. General immunization of children without further attention as to whether they have been immunized or not will result in complete public health control of diphtheria. For determining the immune status of individuals and small groups, where this information is especially desired, the laboratory test devised by the author is convenient and accurate.

Therapeutic Results with Concentrated Scarlet-fever Antitoxin.—DICK and DICK (*J. Am. Med. Assn.*, 1925, **85**, 1693) state that the scarlet-fever antitoxin may be refined and concentrated by the method used in the concentration of diphtheria antitoxin, with an increase in potency and a reduction in serum reactions. In the concentrated and standardized antitoxin the disadvantages of the antistreptococcic serum have been overcome. The basis of the standardization of the antitoxin is the skin-test dose of toxin. It has been found that 1000 skin-test doses of toxin is an amount capable of producing transient symptoms of mild scarlet fever in susceptible adults, if given without any previous immunization. An amount of toxin sufficient to neutralize twenty times this quantity of toxin has been found to be an effective therapeutic dose. Since it is undesirable to inject large quantities of even refined serum, a minimum potency requirement has been established. This requirement is such that one therapeutic dose shall not exceed 20 cc. in volume. The prophylactic dose should be one-half of the therapeutic dose. Smaller amounts may protect moderately susceptible persons, but highly susceptible persons require the larger prophylactic dose for complete protection. The antitoxin is put out in therapeutic and in prophylactic doses. The authors inject the material into the muscles on the anterior aspect of the thigh. They feel that the time saved by intravenous injection of the dose does not compensate for the increased danger. In early cases the

rash is the most convenient indicator of the action of the antitoxin. If enough of the antitoxin is given the rash will be definitely faded within twenty-four hours, and there will be a marked improvement in the general condition of the patient, especially noticeable in the most toxic cases. The improvement will be associated with a fall in temperature. Following the removal of the toxic elements of the disease, the subsequent course of the temperature will depend on the presence or absence of complications. One effect of the antitoxin is the unmasking of such complications as already exist, making their recognition and proper treatment more certain. Of the 34 persons with positive skin tests and scarlet-fever streptococci in their throat cultures, following direct exposure to scarlet fever, who were given one prophylactic dose, 14 had sore throat and fever at the time the antitoxin was given. In 4 a rash was just beginning to appear. None of these 34 susceptible persons already infected with scarlet-fever streptococci developed scarlet fever. They also did not develop any complications. These results indicate that the prophylactic use of scarlet-fever antitoxin in sufficient amounts protects even after the infection has occurred. In the 64 cases of scarlet fever in which one therapeutic dose was given on the same day that the rash developed, no further administration of antitoxin was required. The rash was definitely gone, and the general condition was improved within twenty-four hours. Otitis media occurred in 1 case. No other complications or sequelæ developed in these patients who received antitoxin on the first day of the rash. Otitis media occurred in 5 of the 59 patients who did not receive antitoxin until the second day of the rash. Mastoid infection followed in 1 of these cases of otitis media. No postscarlatinal nephritis occurred in any case in which the antitoxin was given early. Antitoxin was not given after the third day of the rash to any but those patients who had become progressively worse during the first days of the disease, and were not seen until the end of the first week of illness. With one exception, all the deaths in the antitoxin series occurred in persons who had been ill from six to ten days before the antitoxin was administered.

Respiratory Catarrh in Children.—CLARKE (*Lancet*, 1925, ii, 864) noted that half of the children that he examined in routine examination had respiratory catarrh. These infants were from three to six weeks of age. He thinks that the development of respiratory catarrh probably depends on these two factors: The number and virulence of the catarrhal organisms which attack the mucous membrane, and the local resistance of the mucous membrane and the general immunity of the body. It has been shown that the mucous membrane secretes a definite bacteriolytic agent. It would seem from clinical observation that the very young mucous membrane is deficient in resistance, and that mucous membrane that has been the object of early and repeated attacks either loses or never acquires an adequate resistance. The mother and the germ-laden atmosphere are the sources of infection. To prevent infection, if the mother has acute catarrh when the baby is born, she should be instructed to wear a folded handkerchief over the mouth and nose while attending or feeding the baby. This precaution should be extended to the maternity nurse and children's nurse. All

persons coming in contact with the infant should be requested not to breathe on or kiss the baby. To avoid the other main method of infection, the germ-laden atmosphere, is an easy matter in an uncrowded house. The infant should either be kept outdoors or in a draft. It is difficult to overcome predjudice in this matter, especially during the daily bath, but the author says that it is certain that no infant can come to any harm if efficiently bathed in front of a fire with all the windows open. Children should be kept away from people with colds, and children's parties should be cut down to a minimum.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Treatment of Ulcus Molle and Serpiginosum.—In discussing a paper by Gross which mentions the very satisfactory results obtained by the use of Paquelin's cautery in this very resistant condition, BUSCHKE and LEISSNER (*Dermat. Wchnschr.*, 1925, **80**, 544) praised particularly the curative results obtained with solutions of pyrogallic acid in gradually increasing concentration which was effective in one of their cases, even after every other method had failed. The concentration of pyrogallic acid may be gradually increased until the pure acid is used. Late and highly resistant cutaneous syphilids may be successfully treated by this technic. It is interesting to note that no Ducrey bacilli could be found in the lesions studied by the authors. The pronounced factor of individual resistance was well illustrated in one of their cases, in which the woman by whom the male patient was infected had a small chancroid which healed rapidly, while the patient himself developed the highly resistant and extensive serpiginous lesion.

Histopathologic Changes in the Central Nervous System in Pemphigus.—SCHREINER (*Dermat. Wchnschr.*, 1925, **81**, 1559) reviews briefly the three groups of theories as to the etiology of pemphigus: The infectious theory, the bacterial intoxication theory and the autointoxication or metabolic theory. A number of authors have recently concerned themselves with metabolism and blood changes in pemphigus, and Eppinger in particular has found in 3 out of 6 cases changes in the spinal cord. He felt, however, that these could not be regarded as necessary associates of the disease process. Kraus and Huber detected changes in the brain as well as in the spinal cord. Bargum observed isolated changes in the peripheral nerves, but none in the spinal cord.

The author states that his observations are comparable to those of de Crinis, who studied particularly the alterations of the nervous system in severe metabolic disturbances, including particularly diabetes, eclampsia, epilepsy and experimental acidosis. Abnormalities in the staining qualities of the lipoid substance in the nerve tissues and morphologic changes in the glia and ganglion cells were observed. In the author's case of pemphigus Nissl preparations from the cornu ammonia showed an increase in the number of glia cells with regressive nuclear changes. The ganglion cells showed definite signs of disintegration. In other preparations it was possible to demonstrate a marked increase in glia fibers with lipoid droplets in the ganglion cells. The author takes the conservative view that a considerable series of studies will be necessary to establish the connection between such changes and the general pathology of pemphigus.

Observations on the Pharmacology and Toxicology of Bismuth.—HECKELMANN (*Dermat. Wchnschr.*, 1925, **80**, 546), in discussing this topic, states that bismuth line in the gums is observed in 27 per cent of hospital patients and 8 per cent of those in private practice, and stomatitis occurs in 10 per cent of hospital patients as compared with 4 per cent in private practice. The discoloration is due to the formation of bismuth sulphid from the combination of the metal with hydrogen sulphid produced by bacterial decomposition in the mouth. A fatal case of grave stomatitis has been reported by Smechula and a second by Criado. In order to prevent renal complications Felke advises that if 0.3 to 0.4 gm. have been given in ten to fourteen days an interval of two weeks be allowed to elapse before the drug is resumed. No renal irritation is likely to appear until the total dose exceeds 1 to 1.5 gm. Betz has observed that the hematopoietic effect of bismuth is very similar to that of mercury. Erythrocytes decrease after the first injections gradually to 3.1 million and then gradually increase. The hemoglobin may diminish as much as 25 per cent, but again gradually rises. There is an early neutrophilic leukocytosis. The author cites a case of apparent idiosyncrasy on the part of the heart to the use of bismuth reported by Görl and Voigt, in which profound cardiac anxiety, tachycardia and irregularity with prolonged depression, sleeplessness and headache followed a single dose of 0.4 gm. Among the cutaneous complications a purpuric erythema is reported with severe stomatitis and recovery. The blood picture in this case is not described.

Bleeding Time in Socalled Diathetic Eczema.—In five comparable cases of chronic relapsing eczema in adults in whom the disease had been present since childhood, DESCHWANDEN (*Dermat. Wchnschr.*, 1925, **81**, 1499) reports that there was a striking increase in bleeding time, averaging 56.8 minutes as compared with 36.4 minutes normal.

Chromolytic Studies of the Spirocheta Pallida.—To the very interesting problem of the organic constitution of the Spirocheta pallida MÜHLPFORDT (*Dermat. Wchnschr.*, 1925, **81**, 1531) applies the methods of microchemistry, with particular reference to the attack upon it with the aid of dyes. His conclusions are substantially as follows: The Spirocheta pallida has a very complex chemical structure in which the

most important single item is a lipoprotein (confirming the findings of Schumacher). There are, however, no free lipoids in the Spirocheta pallida. In addition to the above-mentioned lipoprotein, chromolytic study of the organism shows that it consists of an outer layer of an acid-containing protein (containing nucleinic acid in an albuminous combination) and a basic protein substrate. No peroxydase could be detected. Any dye which will react chemically with the foregoing elements can stain the Spirocheta pallida. In particular Victoria blue 4 R is able to stain the lipoprotein, and the same property is inherent in other basic triphenyl methane dyes. The particular group in the triphenyl methane dyes which reacts with the lipoprotein is the phenyl radical. The Giemsa stain acts upon the albuminous material. The reaction to 3 per cent aqueous methylene blue takes place with the oxygen-containing acid protein combination. The only acid dye which will react directly with the Spirocheta pallida is a concentrated aqueous solution of erythrosin.

Relation between Verruca Vulgaris and Acuminate Condylomata.—Brandes (*Dermat. Wchnschr.*, 1925, **81**, 1583) found that 68 per cent of a group of patients who had acuminate condylomata likewise had common warts on the hands, face or feet. The author believes that pointed condylomata have no necessary etiologic relation to gonorrhea. He reviews elaborately the literature demonstrating the autoinoculability of verruca vulgaris. This is paralleled by the review of the literature dealing with the autoinoculability of the pointed condyloma. From the collected observations a very fair case is made for the homology if not the identical etiology of the two processes.

The Odor of Arsphenamin.—Leibholz (*Dermat. Wchnschr.*, 1925, **81**, 1602), in discussing the observations of Thurzo on the odor of ether observed by patients receiving arsphenamin and neoarsphenamin, especially the latter, states that the dissolving of neoarsphenamin in water at blood temperature will do away with the odor in the majority of cases. He concedes, however, that there is an element of individual idiosyncrasy over and above the possible ether content of the arsphenamin which must be considered in such cases.

The Action of Arsphenamin in Tabes and Paresis and the Abortive Treatment of Syphilis.—Schumacher (*Dermat. Wchnschr.*, 1925, **81**, 1404) discusses the theory that the failure of arsphenamin to reach the nervous system is due to its insolubility in lipoids. The most interesting detail of the presentation, however, is a condensed summary of the recent literature on superinfection in syphilis in its application to the curability of the disease. Kolle found that it was impossible to produce radical cures of syphilitic rabbits later than ninety days after infection, and that most of the successful cures fall within the first forty-five days. Buschke and Gumpert, Steinfeld, Frei, Brown and Pearce have demonstrated the possibility of superinfection in the rabbit. Buschke and Kroo, in studying the infection of rats with relapsing fever demonstrated the possibility of reinfection in these animals when organisms from the original infection could still be found in the brain. The author concludes that early syphilis is curable with

arsphenamin in man until it has invaded the nervous system. Once this involvement has taken place the inaccessibility of the organisms due to the lipoid insolubility of arsphenamin is such that relapse must be expected.

GYNECOLOGY

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Roentgenotherapy of Uterine Cancer.—BURNAM and NEILL (*Radiology*, 1924, **5**, 1) have recently published a brief review of their experience in the treatment of cancer of the cervix and uterine fundus. Considering first cancer of the fundus, they divide this into three groups, namely: Early, or that in which the uterus is of normal size or slightly enlarged, with no evidence of metastasis; borderline, where the uterus is definitely enlarged with possible lateral thickening without fixation; advanced, where the body of the uterus is a fixed mass in the pelvis and metastasis is evident. In the early cases of this group they advise abdominal hysterectomy unless there is considerable vaginal relaxation, when vaginal hysterectomy, especially in older patients, is desirable. An exception should be made when the patient is old or suffering from some organic disease, making the operation or anesthesia dangerous. In such a patient intrauterine radiation up to $2\frac{1}{2}$ gm. hr., treating the entire uterine cavity, is a curative procedure, especially when the disease is limited to the endometrium. For this they use radium emanation. If after two months there is still discharge, the patient should be examined with a curet, and if diseased is retreated with about one-half the original dose. In the borderline cases they strongly advise abdominal hysterectomy; efficient radium application is difficult to attempt, and on account of the size of the uterus the mechanical difficulties of the vaginal hysterectomy are very marked. When operation is contraindicated for any reason, intrauterine radiation of 3 gm. hr. or more, combined with external through-and-through treatment, is indicated, and in a number of cases has yielded great improvement in the patient's health and both bleeding and discharge usually cease. These patients may, after such treatment, live for years in comfort. Rarely can one expect the disappearance of the mass, although it is not uncommon to find no evidence of growth by diagnostic curettage after the treatment. If operation should be decided on later the radium treatment will not make it more difficult than in ordinary cases. In the advanced cases of this group treatment should be palliative only; intrauterine treatment from 1 to 2 gm. hr. combined with moderate external radiation is given. No attempt is made to radiate organic metastases in other

parts of the body unless they are so located as to cause pain. By this method hemorrhage can be controlled, pain relieved and life prolonged. Considering cancer of the cervix, the authors believe that in the early cases the line of procedure is less clear than in the early body cases. It would seem that almost as many patients are curable by radiation as by operation, but it is not clear what advantage the combination of the two methods gives. It is logical to combine them and best as preoperative radiation, but, except for the fact that we do have some recurrences locally in previously healed cases, the radiation should be discontinued, as it is fraught with considerable danger and is not to be dissociated from morbidity and a marked mortality. Early cases, however, if good risks, should have a small primary death rate, but patients presenting serious organic complications should be radiated and not operated upon. They believe the best time to operate is during the week of the treatment, preferably the very next day, so that there will be no increase in technical difficulty. On the other hand, if operation is delayed there is a definite sclerosis of the tissues making the operation much more difficult. They prefer the abdominal operation, and do not hesitate to implant radium emanation points if the glands are found involved. They do not believe in postoperative radiation with radium unless there is vaginal or local pelvic recurrence. In the borderline cases it is probable that there will be a more general combination of surgery and radiation than in the early cases. If it is found urgent that these cases be radiated, to meet an emergency at the time of operation it is done by the implantation of emanation. They use the radium on a flat applicator, and in neither the early nor the borderline cases do they advise implantation of the parametria through the vagina. Where radium alone is used they give $3\frac{1}{2}$ gm. hr. in a single treatment. They prefer the single dose to the broken dose, as it seems to give very little upset, admits of much more accurate placement and takes less radiation. The second treatment is not to be considered under eight weeks, and only then if there is a definite new development beyond the site of the original disease.

New Method of Sterilization of the Female.—All the previous operative methods for the performance of sterilization of the female have required a laparotomy with the danger that necessarily accompanies such a procedure. Moreover, if it later becomes desirable to reëstablish the possibility of conception a second abdominal operation must be performed. To overcome such drawbacks a new method of sterilization has been proposed by HAENDLY (*Zentralbl. f. Gynäk.*, 1925, **49**, 2404). The method depends upon the formation of a double vagina, and is carried out somewhat in the following manner: Long incisions are made through the vaginal mucous membrane on both sides of the cervix, beginning at the level of the os and running down to the vaginal inlet, ending about $1\frac{1}{2}$ to 2 cm. behind the urethral orifice. The vaginal mucous membrane is dissected free anteriorly and posteriorly to such an extent so that the flaps can be brought together in the midline without too much tension. An oval incision is made on the posterior wall of the cervix and the edges of this incision are sutured on each side with the edges of the anterior vaginal flaps, so that the cervix is united with an anterior vaginal canal. The posterior vaginal flaps on each side are then united to each other, thus making a second vaginal

canal behind the anterior one. The anterior canal, the orifice of which lies just under the urethral orifice and is so narrow that only a catheter can pass through it, serves as an exit for the discharges from the uterus and cervix. The posterior vagina, which is nothing more than a blind sac, is wide and serves the purposes of coitus. If, at a later date, it is desirable to reëstablish the possibility of conception, all that will be required is a long incision through this newly formed septum with suture of the edges on each side, thus reëstablishing the original vagina. The operation can be performed under local anesthesia, which is a big point in its favor, because it must often be performed on patients who are suffering from heart or lung disease and who ordinarily might not stand the danger of an operation.

New Round-ligament Operation for Uterine Retroversion.—New round-ligament operations, like the poor, are always with us, and it would indeed be a rather dull year that the gynecologic literature did not record a half dozen or more "new" operations of this type. However, once in a while, we feel that we must call attention to one of these operations so that we shall not be accused of being too conservative. The operation described by CARRINGTON (*Surg., Gynec. and Obst.*, 1925, **41**, 507) consists of dividing the round ligament between ligatures at a point about midway between the uterus and the internal ring. A small incision is then made in the rectus sheath and another in the anterior leaf of the broad ligament below the division in the round ligament. Then, as in the Simpson operation, a clamp or pedicle needle is passed through the incision in the rectus sheath, carried extraperitoneally to the incision in the broad ligament, is then attached to the free end of the upper half of the round ligament, and on being withdrawn it pulls the round ligament to the rectus sheath, where it is sutured. The distal portion of the round ligament in the lower pelvis is then slid over the proximal portion, care being taken not to strip back the broad-ligament peritoneum from the round ligament. The free end of the distal half of the round ligament is then sutured to the anterior surface of the uterus and the broad-ligament peritoneum attached to it also sutured to the uterus. The proximal and distal halves of the round ligament are then sutured together for the distance that they lie parallel and in close proximity to each other. The procedure can be varied by perforating the broad ligament and carrying the distal portion of the round ligament through the perforation and then suturing it to the posterior surface of the uterus, thus performing a sling operation, similar to the Baldy-Webster operation.

RADIOLOGY

UNDER THE CHARGE OF

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Further Obserations on the Roentgen Diagnosis of Bronchiectasis.—MOORE and MARQUIS (*Am. J. Roentgenol. and Radium Therap.*, 1925,

13, 545) classify bronchiectasis into three groups of arbitrary division. The linear type, the earliest stage and characterized by increase in the linear markings along the terminal bronchi, is usually localized in the lower lobes. This stage is easily overlooked. The second group is the cylindrical type, characterized by a more marked increase in density along the course of the bronchi, with the density fan shaped and interspersed with clearer areas. This type is most common. The third type shows sacculation and is the most advanced. Roentgenologically it is recognized by large pseudocavitations and a marked increase in fibrous elements of the bronchial tract. As in the second stage, drainage by forced coughing and lowering of the head immediately before examination greatly aids the roentgenologist. Bronchiectasis is seen more often now because of more thorough postmortem examinations, and its increased incidence following influenza epidemics, irritation of gases of warfare and fibrosis due to roentgenotherapy. The cough and expectoration are most common symptoms, but are often overlooked by the patient. In the absence of tuberculosis hemoptysis is a very common symptom of bronchiectasis. Although there is a wide divergence of opinion concerning the value of the roentgenologic examination, careful examinations, conservatism in reports and the collaboration of the roentgenologist and the internist have made the Roentgen-ray examination of the utmost importance in the diagnosis of bronchiectasis. Robertson, of the Mayo Clinic, has pointed out that a person suffering from bronchiectasis is a very poor risk for any procedure that necessitates the prone position for any considerable length of time, and this emphasizes the importance of the diagnosis of bronchiectasis.

Deep Roentgen-ray Therapy of Mammary Carcinoma.—The results of deep Roentgen-ray therapy in breast carcinoma, according to EVANS and LEUCUTIA (*Am. J. Roentgen. and Radium Therap.*, 1925, **14**, 135), have been sufficient to establish this form of treatment as a valuable aid in the care of breast carcinoma. They find that the manner of dissemination is one of the most important factors determining the outcome of the disease. This dissemination may be by embolic invasion of the lymph vessels and glands and extension by continuity by way of permeation of the lymph plexuses around the primary lesion. In last stages there may be embolic spread by the blood stream. All operable cases should be operated first and then immediately (eighth to twelfth day) followed by intensive postoperative Roentgen-ray treatment. In the series of 65 cases treated by the authors there has been no recurrences within the area treated in those cases given postoperative radiation of sufficient amount. The treatment aims to cover all possible areas, bearing in mind the permeated cancer area surrounding the lesion, which in some cases may extend 12 to 16 inches from the focus. The dosage must be sufficient to injure the carcinoma cells without injury to the normal tissues, and care must be taken not to produce severe fibrotic changes in the intrathoracic structures. This optimum dose has been found to be 90 to 100 per cent S.U.D. The authors advise against "carcinoma-killing doses." Their method is to use the very penetrating "hard" ray which will allow a more homogeneous distribution of the rays in the

tissues exposed. In this way cross-firing becomes unnecessary. The treatment is not repeated unless there is a probability that not all the carcinoma was removed, in which case the suspected area is re-treated in three months and again a third time.

Irradiation in Cancer of the Cervix.—Taussig (*Radiology*, 1925, **5**, 5) reports on 263 cases of cancer of the cervix of the uterus, where radium was used alone or in conjunction with surgery or Roentgen ray, and found that of a total of 100 cases of cancer of the cervix treated up to four and one-half years ago 8 patients are still living. Less than one-quarter, however, of the patients were considered operable or borderline. Radium was used in the form of the element (150 mg.) except for some emanations. Deep Roentgen ray has been used also since 1922. The dosage now being given is from 4000 to 4500 mg., of which at least two-thirds is beta-radiation, with needles or bare silver tubes. The best results have been obtained by giving the total dosage within six weeks, this to be divided into a larger initial dose of 3000 to 3300 mg., followed by a second dose of 1500 to 1800 mg. in four weeks. This has been applied by inserting 50 mg. into the cervical canal, in silver, 25 mg. in silver beneath it and 75 mg. in the form of seven needles encircling the tumor mass. Complications are becoming less common, but must be guarded against very carefully. Postoperative recurrences in the vaginal vault have an extremely grave prognosis. The author has found early operation after treatment to be inadvisable and prefers to wait four or five weeks after radiation. About three weeks after hysterectomy he has found it advisable to give 100 mg. of radium in silver, brass and rubber in the vaginal vault for fifteen to eighteen hours. The value of prophylactic treatment of deep Roentgen ray is as yet not known. In view of the possible transplantation of cancer cells as a result of needle implantation into a cervical cancer, the author lately has preferred to treat these cases primarily with a series of Roentgen rays, totaling 850 ma. minutes, followed by application of radium needles and tube, unfiltered, amounting to 3500 mg. The value of gland metastases treatments is of still questionable and probably at best only palliative. American cures, as shown by statistics, are less than European, which can be explained on several factors, but until cases reach the physician earlier, and less "timbering" is done by those not qualified to treat these cancers, there will not be much lowering of the high death rate from cervical cancers.

Roentgenologic Examination of Normal and Diseased Bronchi after Filling with Lipiodol.—Lenk and Haslinger (*Klin. Wchnschr.*, 1925, **32**, 1533) credit Americans with the first use of a shadow-producing mixture (barium sulphate in oil) for examining the bronchial tree. Yet the method was not widely employed until the French began using lipiodol. Its chief application is in examination for bronchiectasis, and results have been satisfactory. The authors think, however, that many published illustrations of saccular bronchiectasis are really normal cases in which the alveoli have been filled with lipiodol. To prevent filling of the alveoli those writers recommend introducing the medium into the larger bronchi through a rubber catheter, taking

care: (1) Not to anesthetize the smaller bronchi previously; (2) to have the patient breathe only lightly during injection; (3) to avoid high pressure during injection. Fluoroscopic examination is preferable to simple roentgenography. The authors note that lipiodol in the bronchi will be coughed out in a few hours, but if it enters the alveoli it remains for months, disappearing only by absorption. A further observation is the fact that the lipiodol often accumulates, even against gravity along the fissures apparently because of a favorable relation to the main bronchi. This fact might explain the very common beginning of certain diseases, notably pneumonia, along the borders of a lobe.

The Present Status of the Roentgen Treatment of Purpura Hemorrhagica by Irradiation of the Spleen.—In 1920 Stephan reported two cures of purpura hemorrhagica by Roentgen radiation, according to PANCOAST, PENDERGRASS and FITZ-HUGH (*Am. J. Roentgenol. and Radium Therap.*, 1925, **13**, 558), and since that time there has been much discussion for and against this treatment. They report 6 cases in which the results were found to vary considerably. All patients received one-fifth of an erythema dose, the technic being: Open field; skin target distance, 18 inches; voltage, 120,000; 5 ma. filtered through 5 mm. aluminum; time, ten minutes; given from ten days to three weeks apart. One case gave a toxic reaction in the first treatment only; 3 cases showed platelet count increase, whereas the others showed no change. Four cases showed clinical improvement, but some of these had received blood transfusion prior to treatment, and none can be classified as "cured." It is felt by the authors that in order to draw conclusions of value a large series of cases must be carefully studied, and the technic of the blood examination be very closely guarded from the many sources of error. Transfusion of whole or citrated blood has been beneficial, as has been intramuscular injection of whole blood, the benefit resulting probably from the protein shock. Splenectomy has given the best results to date, and it suggests the possibility of good results from "massive" irradiation, of which experiments are now being performed. The authors append to their article an abstract of their exhaustive bibliography of the literature concerning the effects on the blood of splenic radiation.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Syringomyelia in Association with Acromegaly.—Cases are cited from the literature and grouped: (1) Not true acromegaly; (2) doubtful

acromegaly; (3) genuine acromegaly. Another group of cases is mentioned in which changes around the central canal of the spinal cord were found in acromegalics, but without physical signs so far as was known. McBRIDE (*J. Neurol. and Psychopath.*, 1925, **6**, 114) presents two cases with definite acromegaly and syringomyelia. Previous work points to the supposition that acromegaly precedes the syringomyelia. A theory is presented for the association of the two diseases. It has been observed that splanchnomegaly sometimes accompanies acromegaly, and it is presumed that such may take place in the cord with selective action on the ependymal cells of the cental canal ending in a gliosis.

On Brains with Total and Partial Lack of Corpus Callosum and on the Nature of the Longitudinal Collosal Bundle.—A case history is presented by DE LANGE (*J. Nerv. and Ment. Dis.*, 1925, **62**, 449) of a child that died at five months of age, in which autopsy revealed total absence of corpus callosum. The brain is carefully described. The microscopic anatomy is compared with the anatomy of a normal brain of the same age. It is thought the brain without a callosum resembled a Simian brain in configuration. Literature and etiology are discussed. Persons without a corpus callosum usually have mediocre or less intelligence, though apparently normal persons may have some agenesis of this structure. Some of such cases seem to have been "short tempered." What part the corpus callosum plays in coördinated movements of both sides of the body is not fully established.

Effect of Organic Brain and Spinal-cord Changes on Subarachnoid Space, Choroidal Plexus and Cerebrospinal Fluid.—Sections from the malignant tumors of the meninges are presented by HASSIN (*Arch. Neurol. and Psychiat.*, 1925, **14**, 468) to show that the brain is not invaded by such tumors, but the pia or arachnoid continue to be infiltrated. In meningitis the inflammation rarely invaded the brain. In brain softenings lipoids are carried to the ependymal layer and perivascular spaces. In a section of the cord from a case of poliomyelitis hematogenous elements seem to have been carried to the central canal. A section from a case of solitary tubercle of the cord shows the dura involved in the tuberculous process. The course of the infectious process seems to have been toward the surface of the cord. The works of Weed and Foley are discussed. The author favors the theory that the cerebrospinal fluid comes from the brain and cord tissue and that the choroid plexus and the villi are organs of excretion.

"Word Blindness" in School Children.—Most of the material was collected by ORTON (*Arch. Neurol. and Psychiat.*, 1925, **14**, 581) at an experimental clinic held in Green County, Iowa. Among the children who were reported as dull, failing, or retarded, by their teachers, were a large number whose greatest disability was learning to read. Three of this group were especially studied, and 1 (M. P.) was admitted to the Iowa State Psychopathic Hospital. In all 142 grade and high-school pupils were studied, and 88 of this group were referred by teachers because they were considered deficient. Eighty-four of the 88 gave intelligence quotients ranging from 25 to over 120. M. P., aged six-

teen years and two months, had a mental age of eleven years and four months; intelligence quotient, 71 (by the revised Stanford-Binet test). He seemed to be intelligent along mechanical and nonverbal directions, but had the greatest difficulty in reading and writing compositions. When certain alternative tests were used in the Stanford-Binet test his mental age was thirteen years and ten months; intelligence quotient, 86. In the head aphasia tests he named objects presented, and recognized them readily, but when he had to pronounce the name of an object presented he hesitated and made many mistakes. Reading was labored and slow. Copying was difficult; writing to dictation was done well. In copying many neographisms were apparent, and in reading neologisms or distortions of a particular type were frequent. It was apparent that he could respond to training, but only slowly, and the training required was of a very special nature. Fourteen other cases who had difficulty in reading were studied. These often presented the difficulty of distinguishing a lower case p from q or b from d, or confused on with no, or not with ton. Some of them could read from a mirror image as well or even better than from the printed page. The case of a woman is cited who was considered different from her family and less intelligent. She was observed to spell her words and reverse the direction of her words. Some evidence is given to show that left-handedness is more frequent in people with such disabilities; also stuttering, which occurred in 3 of 15 cases studied, and some undefined speech defect was present in 4 others. Fourteen of the 15 were boys. They showed more than average motor incoordination. The author presents some evidence from old inscriptions to show that the tendency to read in either direction, that is, from left to right or right to left, was present. He says that our system of print, favoring right-handed people, causes the impressions which get to the right visual hemisphere to be ignored. In a few the impulses from the right hemisphere cannot be ignored, and thus reading or writing interferences develop when the stimuli are visual. Three definite visual areas of the brain are presented, namely: Visual perception, visual recognition and visual association. Bilateral destruction of the first two of these are necessary for word blindness, but unilateral defect of the last would produce a degree of word blindness. Interesting charts are presented. The author names this new disorder strephosymbolia. The psychiatric sequelæ of these disabilities are: (1) Contented apathetic disregard of handicap; (2) mild paranoid reaction toward teachers; (3) development of feelings of inferiority; (4) emotional blocking. Some efforts are being made to devise the best training methods for persons with such defects.

Epilepsy as Symptom of Disseminated Sclerosis.—Literature is cited which discusses this problem by WILSON and MACBRIDE (*J. Neurol. and Psychopath.*, 1925, **6**, 91), presenting eight cases. The following clinical varieties are mentioned: (*a*) Epileptiform attacks (Jacksonian); (*b*) epileptic attacks (generalized convulsions); (*c*) with petit mal attacks; (*d*) with "epilepsia-partialis continua." The various theories of pathogenesis are discussed, but no autopsy material was presented. The authors favor the view that disseminated sclerosis may possibly cause epileptic phenomena by cortical irritation.

Reactive Gliosis in a Case of Brain Tumor.—FREEMAN (*Arch. Neurol. and Psychiat.*, 1925, **14**, 649) discusses the enlargement of the hemisphere on the side of tumor as due to: (1) Increase in substance; (2) vascular disturbances; (3) reactive gliosi. The gliosis is apparently most marked near the tumor, but is usually present at considerable distance from the tumor. A brain with a tumor in the extreme left frontal lobe was studied. A special neuroglia stain (Cajal) was used. The neuroglia cells were counted in sections from several areas from both hemispheres symmetrically located. In every case the left hemisphere (side of tumor) had more neuroglia cells. The neuroglia cells nearest the tumor also showed hypertrophy.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
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Intranuclear Inclusions in Visceral Disease.—The presence of intranuclear bodies with specific tinctorial properties has been widely accepted as indicative of infection with a virus having special affinity for tissues of neural or ectodermal origin. VON GLAHN and PAPPENHEIMER (*Am. J. Pathol.*, 1925, **1**, 445) report a case with an anatomic diagnosis of abscess of the liver, ulcerative colitis with hemorrhage, suppurative pleurisy, lobular pneumonia and bronchiectasis. Cells containing intranuclear inclusions were found in the bases of the colic ulcers, in the wall of the hepatic abscess and in the alveoli of the lung. The authors bring forward for consideration the possibility that viruses of this type may localize in tissues other than skin and central nervous system. They also suggest that the virus related to these inclusion cells was concerned in producing the lesions found in the colon, liver and lung in this case.

Progressive Alcoholic Cirrhosis.—HALL and OPHÜLS (*Am. J. Pathol.*, 1925, **1**, 477) report 4 cases of early alcoholic cirrhosis. The history of all 4 patients revealed chronic alcoholism and alcoholism was the principal cause of death in 2 of them. In no case was the cause of death directly related to the liver cirrhosis. All 4 livers were above normal in size. Microscopically there was evidence of damage to liver cells, as shown by failure of nuclei to stain along with hyaline granules and vacuoles in the cytoplasm. Accompanying this was a marked infiltration of leukocytes, lymphocytes and young fibroblasts. Signs of regeneration of liver cells and bile ducts were evident in all cases. In no case was any organism demonstrated in the liver tissue. The authors suggest that the same toxic agent which caused the liver necrosis was also the stimulus for the proliferation of fibroblasts.

Observations on Focal Tuberculin Hypersensitiveness in an Infected Organ Previous to a General Sensitization—STEWART (*Am. J. Pathol.* 1925, **1**, 495) investigated this subject by injecting 0.1 cc. of a saline suspension containing 2.5 mg. per cubic centimeter of living bovine tubercle bacilli in the right testis of a series of normal guinea pigs. On the second, third, fourth, fifth, sixth, seventh and eleventh days following this 0.1 cc. of a 5 per cent old tuberculin was injected into both testes and also intradermally. The following results were noted: (1) The infected testis reacted to the tuberculin before any reaction elsewere; this occurred within twenty-four hours and was manifested by a focal desquamation and degeneration of the tubular epithelium, cessation of spermatogenesis and a surrounding leukocytic infiltration; no skin reaction occurred and the other testis was normal. (2) On the sixth day the control testis showed some focal reaction to the tuberculin. (3) The intradermal test did not become positive until the eleventh day. Control animals injected with physiologic saline did not give the same picture.

Experimental Glomerulonephritis.—BULL, CLAWSON and HARTZELL (*Am. J. Pathol.*, 1925, **1**, 247) claim that of the four types of renal disease found in man, namely: (1) Exudative interstitial nephritis, (2) nephrosis, (3) arteriosclerotic kidney and (4) glomerulonephritis; only two had so far been produced in laboratory animals. These have been the exudative interstitial nephritis and nephrosis. They experimented with rabbits and monkeys, using both hemolytic and nonhemolytic strains of streptococci. The streptococci were obtained from human lesions, were grown on blood agar about twenty-four to forty-eight hours, and suspensions made with physiologic salt solutions. Nonhemolytic strains were generally used, and injections were made intravenously. With the rabbits they were able only to produce a few cases of interstitial nephritis and a few of nephrosis. They also used 14 young rhesus monkeys and obtained 2 cases of severe nephrosis, 1 of acute interstitial nephritis and 1 of a glomerulonephritis. The kidneys in this last case were moderately enlarged, with slightly adherent capsules. The cortices were opaque and no markings were visible. The surfaces were finely granular. Microscopically most of the tubules showed a definite reduction in size, and those attached to damaged glomeruli showed a pronounced atrophy. Five to 10 per cent of the glomeruli showed epithelial crescents, and many showed fusions between the glomerulus and the outer layer of Bowman's capsule. Many glomeruli had part of the capillary network occluded by swollen endothelial cells, and there were a few examples of exudative glomerulitis. They conclude that they have been successful in producing glomerulonephritis in this monkey.

The Origin of the Mononuclear Phagocytes of Peritoneal Exudates.—The peritoneal exudates investigated by MCJUNKIN (*Am. J. Pathol.*, 1925, 1, 305) were produced by injections of india ink, trypan-blue solutions and whole rabbit's blood into the peritoneal cavities of normal rabbits, splenectomized rabbits and rabbits receiving intravenous injections of india ink. The exudates were examined on filmed slides made by the method for supravital staining of Pappenheim and

Simpson. The author describes three types of mononuclear phagocytic cells: The "hyaline" cells, with a variable affinity for neutral red; "rosette" cells, with neutral red in wreath form; "nonrosette" cells, with the dye granules scattered diffusely in the cytoplasm. To determine the origin of these he examined the tissues and organs from normal, trypan blue and india ink rabbits, first in fresh preparations supravitally stained and second in paraffin sections of supravitally stained tissues. He believes that the "hyaline" cells come from the vascular endothelium. The "rosette" cells arise from the reticuloendothelium of the lymph glands, while the "nonrosette" cells seem to have a double origin, coming from either the lymph glands or the endothelium of the bloodvessels.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Relationship of Hard Water to Health: II. Effect of Hard Water on Growth, Appearance and General Well-being.—MYERS' (*J. Infect. Dis.*, 1925, **37**, 13) studies showed that white mice on a diet of grains and a natural very hard water (520 parts per 1,000,000 of $CaCO_3$) showed no striking differences in growth or appearance from those on a similar diet receiving distilled water. White rats on a diet of bread, milk and yellow corn meal exhibited no marked differences. Young rabbits on a diet of oats, carrots and alfalfa and the natural hard water were about 30 per cent heavier at the age of forty-two days than similar rabbits on distilled water. A few dogs on a mixed diet and the natural hard water grew faster and had a better general appearance than similar dogs with distilled water. Two calves on a diet of milk, oats, corn and alfalfa and a moderately hard water (200 parts per 1,000,000 of $CaCO_3$) were 20 per cent heavier at the age of eight months than a similar pair which had received only distilled water. Several groups of chicks on a grain diet and the natural hard water gained from 20 to 40 per cent more during the first few months of life than did similar groups on a distilled-water intake. Distilled water to which had been added as nearly as possible the same salts as were in the natural hard water gave practically the same results with chicks as did natural hard water. The same was true of distilled water containing 400 to 100 parts per 1,000,000 of calcium carbonate and of distilled water containing 2000 parts per 1,000,000 of calcium chlorid. Distilled water containing 200 parts per 1,000,000 of Na_2HPO_4 increased the rate of growth of chicks as much as did calcium. Two hundred parts per

1,000,000 of NaCl had no effect on growth of chicks. On a synthetic diet containing the essential foods, and including cod-liver oil, chicks receiving distilled water grew at the same rate as those receiving the natural hard water, or distilled water containing $CaCO_3$ of $CaCl_2$. The urinary output of calcium and phosphorus in rabbits was apparently not affected by the salts in hard water. In no instance did animals on distilled water develop better than those on hard water, but the reverse was true under several conditions.

Extraordinary Dormancy or Delayed Germination of Spores which have been Subjected to Heat.—The report by DICKSON and others (*J. Infect. Dis.*, 1925, **36**, 472) deals with a series of observations on the thermal death time and germination time of botulinus spores based on a study of approximately 37,000 sealed-tube preparations which have been under inspection for from twenty-eight to thirty-nine months after the spores were heated. The maximum dormancies recorded are thirty-seven months for spores which were heated and incubated in oil stratified broth, twenty-two months for spores which were heated and incubated in broth without oil and eleven months for spores which were heated and incubated in agar. The maximum survival times and the greatest dormancies were observed in tube preparations in which the spores were heated and incubated in broth medium which was covered with a thin layer of mineral oil. Attention is directed to the practical application of these facts to the preservation of foods.

A Plan to Establish in the United States a Morbidity Registration Area, That is, an Area for the More Complete Collection of Data Relating to the Diseases of Man —LLOYD (*Pub. Health Rpts.*, 1925, **40**, 1549) states that a comparison of morbidity rates from various communities is important if proper evaluation of data is to be made. To best accomplish this, reports must be made to a central sanitary authority and must include at least diphtheria, influenza, pneumonia, poliomyelitis, scarlet fever, smallpox, tuberculosis, typhoid fever and whooping cough. The reports would be checked from time to time by agents of the central coördinating unit. Requirements are suggested for specific diseases.

The Rat Proofing of Vessels.—GRUBBS (*Pub. Health Rpts.*, 1925, **40**, 1507) points out the desirability of rat proofing of vessels from the sanitary and economic points of view in order that food and drink may be made inaccessible and hiding and nesting places abolished: "(1) All foodstuffs, whether new or garbage, should be in rat-proof containers or kept within rooms devoid of rat harborage and into which rats cannot come from without. (2) All small inclosed spaces should either be abolished or, if this is not possible, should be blocked off by material impenetrable to rats at all points where a rat may get a foothold in order to gnaw through. (3) Large openings should be closed by screening or by doors or windows that fit and that are impenetrable to rats at gnawing levels, and they should be kept closed; all small openings should be permanently screened or closed." General specifications are given and illustrations are provided.

PHYSIOLOGY

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SESSION OF DECEMBER 14, 1925.

Trichomonas Buccalis.—M. J. Hogue (from the Department of Anatomy, University of Pennsylvania Medical School). The protozoan flagellate, Trichomonas, was first found by Donne in the human vagina in 1837. Since then it has been found in the mouth and in the intestines. These forms have been called Trichomonas buccalis, Trichomonas hominis and Trichomonas vaginalis, according to their source. Some investigators consider them as three distinct species, others as one or two species. More information is needed before this point can be settled. With this end in view the present work was begun. Trichomonas buccalis has been studied both culturally and microscopically and compared with Trichomonas hominis, the form found in the intestine of man. Both Goodey (*J. Parasitol.*, 1917, **9**, 537) and Ohira and Noguchi (*J. Exper. Med.*, 1917, **25**, 341) published short accounts of this form, and called it Tetratrichomonas buccalis. Since then Trichomonas has been established as the generic name, so the form in the mouth is known as Trichomonas buccalis. During the past year I have found Trichomonas buccalis in nine persons in the scrapings from the teeth near the gums. It is present in the upper and lower jaws of men and women, both whites and negroes. The strains isolated came from persons with histories of pyorrhea, gingivitis and abscessed teeth. It was cultured for over seven months, with more than 110 transfers. The cultures were discontinued during the summer months, though the organisms were in excellent condition at that time. The culture medium was a mixture of equal parts of sterile sodium chlorid solution (0.85 per cent) and sterile sheep serum water (1 part of serum to 3 parts of water). Tubes of this were enriched with a small amount of saliva. They were incubated at 30° C. The strains were compared as to their vitality, their thermal death point and their sensitiveness to hydrogen-ion concentration. Slight differences were noticed in the various strains. When Trichomonas buccalis was compared with Trichomonas hominis, the form in the intestine of man, it was found that they grew on a culture medium differing in the amounts of serum and kinds of serum used. Also that Trichomonas hominis thrived on Locke egg medium and ovomucoid medium, while Trichomonas buccalis grew slightly on ovomucoid and not at all on Locke egg. Morphologically, the most striking difference was that pointed out by Goodey and by Ohira and Noguchi, that is, Trichomonas hominis has a free flagellum at the posterior end of its undulating membrane, while Trichomonas buccalis has no free flagellum at this point. All the nine strains of Trichomonas buccalis studied had four anterior flagella. They also had mitochondria and neutral red granules.

The Influence of Change in Temperature on the Location of the CO_2 Absorption Curve of Blood and Serum.—W. C. Stadie, J. H. Austin and H. W. Robinson (from the John Herr Musser Department of Research Medicine, University of Pennsylvania). In the study of the acid-base equilibrium of blood almost all investigations have thus far been conducted at some one temperature, and the interrelations of CO_2 tension, CO_2 content, oxygen tension, oxygen saturation, variations in fixed acids and bases, such as sodium, potassium, chlorids, phosphates and organic acids at one temperature, have been fairly well defined. The effect of change of temperature upon these interrelations has been less extensively investigated. The most important effects of change in temperature are: (1) Variations in the solubility coefficients of the gases in blood and serum; (2) variation in the dissociation constant of carbonic acid and, in consequence of this, variation in the relation between the ratio, $\left(\frac{BHCO_3}{H_2CO_3}\right)$, and the pH; (3) variation in the base bound by protein. This study is an investigation of the third of these variations. In normal serums or blood the base is bound by: (1) Strong acids, chiefly chlorid; (2) cell and serum protein, to an extent dependent upon the concentration and type of protein, upon the pH and upon the temperature; (3) approximately the remainder of the base is bound by carbonic acid as bicarbonate. Since in a given specimen of blood or serum (1) is constant and only (2) and (3) vary significantly with pH and temperature, and since (3) is dependent upon the base remaining after the requirements of (1) and (2) are satisfied, it follows that: (*a*) Variations in bicarbonate at varying pH but constant temperature can be used as a measure of change in base bound by serum and cell protein with change in pH; (*b*) that variations in bicarbonate at varying temperature but constant pH can be used as a measure of change in base bound by serum and cell protein with change in temperature; (*c*) that there is a certain change of pH for a given change of temperature which will keep the base bound by protein and hence the bicarbonate constant. We have found experimentally in the whole blood, separated serum and true serum of sheep and dog that the change in pH per °C. change in temperature between 20° and 38° at constant ($BHCO_3$) is from -0.017 to -0.023 pH. The effect of change of temperature is to shift the plot of ($BHCO_3$) against pH toward the alkaline side with fall in temperature without any consistent change in the slope of the plot. The relation of true serum to its whole blood is not changed so far as our experimental methods demonstrated. The figures stated express also approximately the change in pH of blood or serum as it undergoes change of temperature without change in total CO_2 content. This study is consistent with the observations of Stadie and Martin on the whole blood of man, and extends their calculations of the heat of ionization of cell proteins to serum proteins, indicating that the heat of ionization of both is of about the same magnitude.

The Permeability of the Mammalian Erythrocyte to Certain Ions, with a Description of Two Simple Methods for the Study of Hemolysis.—M. H. Jacobs (from the Department of Physiology, University

of Pennsylvania, and the Marine Biological Laboratory, Woods Hole, Mass.). The mammalian erythrocyte is a very highly specialized type of cell. Among other differences between it and ordinary cells appears to be a free permeability to at least certain anions—a property of much importance in the transport of CO_2 by the blood. The present investigation represents an attempt to throw further light on this difference by contrasting, in certain solutions, the behavior of the erythrocyte with that of the egg of the sea urchin, Arbacia, which resembles it in swelling and giving up its pigment in strongly hypotonic solutions. The solutions employed were: (*a*) NH_4Cl of different strengths and pH, and (*b*) mixtures of CO_2 and $NaHCO_3$ of different pH and CO_2 tensions. In the case of NH_4Cl the osmotic effects with Arbacia eggs were found to be almost the same as those of NaCl and KCl; with erythrocytes they were entirely different. In the case of the CO_2-bicarbonate system, the effects on the Arbacia eggs depended much more on the CO_2 tension of the solution than on its pH as such; with the erythrocytes the reverse was true, the pH being the factor of chief importance. These results are entirely in accord with the view that the egg of Arbacia is relatively impermeable to all ions, while the erythrocyte is permeable to at least certain anions but not in general to cations. In carrying out the experiments on erythrocytes two methods were used which have a number of advantages and do not appear to have been hitherto employed. The first depends on the fact that in experiments on hypotonic hemolysis concentration and pH may be looked upon as two independent variables. In the method ordinarily used the pH is kept approximately constant by the buffers of the rather large amounts of blood added to the solutions, and the concentrations of the latter are made to vary. In the new method, which permits the use of much smaller quantities of blood, the concentration is kept constant and the pH is varied. A convenient solution for normal and pathologic human bloods is one composed of 4 parts of M/13 NaCl + 1 part of M/13 $NaHCO_3$. The pH is adjusted in steps of 0.1 or 0.2 from 6.8 to 8.0 by bubbling in an excess of CO_2 and then slowly removing it with a stream of air, phenol red being used as the indicator. The second method makes it possible to determine the point where hemolysis begins and to follow its course in very dilute suspensions of corpuscles. Its essential point consists in the use of an apparatus by which the thickness of the layer of the suspension which just permits the image of the filament of a carbon lamp to show is read off on a scale, which can then by simple methods be calibrated to indicate percent hemolysis.

The Effect of Hydrogen-ion Concentration on Swelling of Cells.—B. Lucke and M. McCutcheon (from the Pathological Laboratory, School of Medicine, University of Pennsylvania, and the Marine Biological Laboratory, Woods Hole, Mass.). Study of the changes in size in living cells resulting from changes in the composition of the fluid medium in which they exist is fundamentally important both for physiology and pathology. Many investigations of the swelling of non-living material, such as gelatin, have been made and inferences have been drawn, thought to be applicable to living-tissue cells. Erythrocytes, because of their convenient availability, have frequently

served as objects of this sort of study. But it seems definitely certain that results obtained with dead proteins cannot be transferred to living protoplasm, and erythrocytes, from the standpoint of structure, vitality and chemical composition, can hardly be regarded as similar to the majority of animal cells. We have sought to study the effects of acids and alkalies upon the volume of cells which, in structure and composition, more closely resemble tissue cells and which, in addition, can be made to exhibit a definite criterion of life—for only in a cell possessing this latter attribute can one discover whether or not the production of an effect is dependent upon damage to vitality. The cells chosen were unfertilized eggs of Arbacia; they are spherical and hence easily measurable; they behave as if surrounded by a definite membrane; their vitality can be approximately estimated by determining their response to fertilization. In one series of experiments various lots of eggs were subjected to changes in the reaction of the surrounding medium, a pH range of from 3.0 to 9.8 being established by the addition of HCl or NaOH to neutralized sea water. Living eggs did not undergo change in size; only after they were severely damaged, as shown by subsequent fertilization experiments, did swelling occur. Similar results were obtained when CO_2 and NH_4OH were used. Work by others has shown that erythrocytes swell immediately under conditions similar to those which we have tested; this result is interpreted to mean the passage of ions into the cell, with consequent increase in osmotic pressure and attraction of water, in accordance with the permeability of the membrane and the laws of membrane equilibrium as formulated by Donnan. Our experiments show an entirely different response to acids and alkalies on the part of Arbacia eggs, and indicate that as long as the cell is uninjured a "Donnan equilibrium," such as occurs in erythrocytes, is not established in the cells investigated by us.

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